Goldfrank's MANUAL OF TOXICOLOGIC EMERGENCIES

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DEDICATED TO . . .

The staffs of our hospital emergency departments who have worked with remarkable courage, concern, compassion, and understanding in treating the patients discussed in this text and many thousands more like them

The staff of the New York City Poison Center who have quietly and conscientiously integrated their skills with ours to serve these patients; and to the many others who never needed a hospital visit because of the staff's efforts

To my wife Ali, my children Casey and Jesse, my parents, my friends, family, and colleagues for their never-ending patience and forgiveness for the time spent away from them (R.H.)

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Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The editors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the editors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

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Table of Antidotes in Brief

Readers of *Goldfrank's Toxicologic Emergencies* are undoubtedly aware that the editors have always felt that an emphasis on general management of poisoning or overdoses coupled with sound medical management is more important than, or as important as, the selection and use of a specific antidote in the vast majority of cases. Nevertheless, there are some instances where nothing other than the timely use of a specific antidote or antagonist will save a patient. For this reason, and also because the use of such antidotes may be problematic, controversial, or unfamiliar to the practitioner (as new antidotes continue to emerge), we have included a section (or sections) at the end of each chapter where a brief discussion of such antidotes is relevant. The following Antidotes in Brief are included in this edition.

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Preface

The eighth edition of *Goldfrank's Toxicologic Emergencies*, published in 2006, continues to offer readers an approach to medical toxicology based on case studies. The addition of almost 30 new chapters and five Antidotes in Depth, and the elimination of seven other chapters, are a reflection of major advances, changes in understanding, new intellectual approaches, and the ever expanding role of toxicologists at the beginning of the 21st century.

An expanded number of authors and reassignment of more than 15% of the chapters captures new and unique perspectives on toxicology. Critical events and concerns at the turn of the new century led to an expansion of the chapter on chemical and biological weapons, which was new in the seventh edition, to two separate chapters. A chapter on risk assessment and risk communication offers the reader an appropriate context for discussing these issues more effectively and the increasing emphasis on improving our use of medications is reflected by new chapters on patient safety and poison prevention that focus on public health, the potential of medical informatics, and the critical roles that providers play in improving clinical care.

However, as the eighth edition of *Goldfrank's Toxicologic Emergencies* grew to more than 2000 pages and the desire to include extensive supporting graphics and information led to the inclusion of a corresponding website (available at www.goldfrankstoxicology.com with the purchase of the main text), it also became clear that a smaller clinically focused companion text could be valuable to the clinician who needed key information at the patient's bedside.

All of our principles developed in detail in the textbook were adapted for this concise manual of medical toxicology. We have attempted to retain the rigor of the chapters in the main text while at the same time providing a focused approach designed for use both at the bedside and by students and others who may not as yet be fully committed to an in-depth study of medical toxicology. Although this manual is meant to stand alone, it is also a companion work, as only the main text provides extensive supportive background information and the essential citations to the toxicologic literature of the world.

Work on the next edition of *Goldfrank's Toxicologic Emergencies* literally begins the day that the current edition is published. We worked to preserve and respect the enormous personal effort given and rigor achieved by each author in the main text in the condensed contributions presented in this manual. Consequently, the content and style of this companion should be immediately recognizable to users of the previous and current editions of *Goldfrank's Toxicologic Emergencies*.

We hope that this "new text" serves you well. If it helps to provide better patient care and stimulates interest in medical toxicology by students of medicine, nursing, and pharmacy; by residents in emergency medicine, internal medicine, pediatrics, preventive health, critical care, family practice, and others; by fellows in medical and clinical toxicology; and by attending physicians and faculty, graduate pharmacists and nurses as well as toxicologists, then our efforts will have indeed been worthwhile. As always, we encourage your submission of comments and thoughtful criticisms, and we will do our best once again to incorporate your suggestions into future editions.

Robert S. Hoffman
Lewis S. Nelson
Mary Ann Howland
Neal A. Lewin
Neal E. Flomenbaum
Lewis R. Goldfrank

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We are grateful to Joan Demas, with her commitment to detail and exceptional rigor, who not only helped manage the growth and development of the eighth edition and this companion, but also transformed scrawl into manuscript with precision and dedication.

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We thank the many volunteers, students, and librarians, particularly the St. John's University College of Pharmacy students and drug information staff, who provide us with vital technical assistance in our daily attempts to deal with toxicologic emergencies.

No words can adequately express our indebtedness to the many authors and collaborators who worked on the eighth edition of *Goldfrank's Toxicologic Emergencies*. All these authors are recognized as contributors to this effort. As different authors write and rewrite topics with each new edition, we recognize that without the foundation work of their predecessors, our text and this manual would not be what they are today. Although it is impossible to thank all of the earliest contributors, these dedicated individuals are recognized throughout the acknowledgements sections of the eight editions of *Goldfrank's Toxicologic Emergencies*. To the best of our abilities, the efforts of the current authors and their predecessors are faithfully represented in this companion version.

We appreciate the conscientious and tireless work of James Semidey, who has found so many essential articles and prepared so many copies for editorial review.

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1 Historical Principles and Perspectives

The term *poison* first appeared in the English literature around the year 1230 A.D. to describe a potion or draught that was prepared with deadly ingredients. The history of poisons and poisoning, however, dates back thousands of years. Throughout the millennia, poisons have played an important role in human history—from political assassination in Roman times, to weapons of war, to contemporary environmental concerns, and, more recently, to new weapons of terrorism.

CLASSIFICATION OF POISONS

In his treatise, *Materia Medica*, the Greek physician Dioscorides (A.D. 40–80), categorized poisons by their origin: animal, vegetable, or mineral. This categorization remained the standard classification for the next 1500 years.

Animal Poisons

Animal poisons usually referred to the venom from poisonous animals. Although the venom from poisonous snakes has always been among the most commonly feared poisons, poisons from toads, salamanders, jellyfish, stingrays, and sea hares are also of concern. A notable fatality from the effects of an animal toxin was Cleopatra (69–30 B.C.), who reportedly committed suicide by deliberately falling on an asp.

Vegetable Poisons

Theophrastus (ca. 370–286 B.C.) described vegetable poisons in his treatise *De Historia Plantarum*. Notorious poisonous plants included *Aconitum* species (aconite, monkshood), *Conium maculatum* (poison hemlock), *Hyoscyamus niger* (henbane), *Mandragora officinarum* (mandrake), *Papaver somniferum* (opium poppy), and *Veratrum album* (hellebore). Hemlock was the official poison used by the Greeks and was employed in the execution of Socrates (ca. 470–399 B.C.) and many others.

Mineral Poisons

The mineral poisons of antiquity consisted of the metals: antimony, arsenic, lead, and mercury. Although controversy continues to this day about whether an epidemic of lead poisoning among the Roman aristocracy contributed to the fall of the Roman Empire, lead was certainly used extensively during this period.

Gases

Although not animal, vegetable, or mineral in origin, the toxic effects of gases were also appreciated during antiquity. In the 3rd century B.C., Aristotle commented that "coal fumes (carbon monoxide) lead to a heavy head and death," and Cicero (106–43 B.C.) referred to the use of coal fumes in suicide and execution.

RECENT POISONINGS AND POISONERS

Although accounting for just a tiny fraction of all homicidal deaths (0.16% in the United States), notorious lethal poisonings continued throughout the 20th century (Table 1–1). In 1982, deliberate tampering with nonprescription acetaminophen preparations with potassium cyanide caused seven deaths in Chicago. Because of this tragedy, packaging of nonprescription medications was changed to decrease the possibility of future product tampering. The perpetrator(s) were never apprehended, and other deaths from nonprescription product tampering were reported in 1991.

In 1971, a 14-year-old in England killed his stepmother and other family members with arsenic and antimony. Sent away to a psychiatric hospital, he was released at 24 years of age, when he was no longer considered to be a threat to society. Within months he began to engage in lethal poisonings, killing several of his coworkers with thallium. Ultimately, he died in prison in 1990.

In 1978, Georgi Markov, a Bulgarian defector living in London, developed multisystem failure and died four days after having been stabbed by an umbrella carried by an unknown assailant. The postmortem examination revealed a pinhead-sized metal sphere embedded in his thigh where he had been stabbed. Investigators hypothesized that this sphere had most likely carried a lethal dose of ricin into the victim. This theory was greatly supported when ricin was isolated from the pellet of a second victim who was stabbed under similar circumstances.

In 1998, a woman known as the "black widow" was executed for murdering her husband with arsenic in 1971 in order to collect insurance money. She was the first female executed in Florida in 150 years. The fatal poisoning remained undetected until 1983, when she was accused of trying to murder her fiancé with arsenic and by car bombing. Exhumation of the husband's body, 12 years after he died, revealed substantial amounts of arsenic in the remains.

Healthcare providers are implicated in several poisoning homicides. An epidemic of mysterious cardiopulmonary arrests at the Ann Arbor, Michigan, Veterans Administration Hospital, in July and August 1975, was attributed to the homicidal use of pancuronium by two nurses. Intentional digoxin poisoning by hospital personnel may have explained some of the increased number of deaths on a cardiology ward of a Toronto pediatric hospital in 1981, but the exact cause of the high mortality rate was unclear. In 2000, an English general practitioner, was convicted of murdering 15 female patients with heroin, and may have murdered as many as 297 patients during his 24-year career. These recent revelations prompted calls for strengthening the death certification process, for improving preservation of case records, and for better procedures for monitoring controlled drugs.

Also in 2000, an American physician pleaded guilty to the charge of poisoning a number of patients under his care during his residency training. Succinylcholine, potassium chloride, and arsenic were some of the agents he used to kill his patients. Attention to more careful physician credentialing and to maintenance of a national physician database arose from this case because the poisonings occurred at several different hospitals across the country. Continuing concerns about healthcare providers acting as serial killers is highlighted by a recent case in New Jersey in which a nurse was found responsible for killing patients with digoxin.

By the end of the 20th century, 24 centuries after Socrates was executed by poison hemlock, the means of implementing capital punishment had come

TABLE 1–1. Important Early Figures in the History of Toxicology

Person	Date	Importance
Homer	ca. 850 B.C.	Wrote how Ulysses anointed arrows with the venom of serpents
Socrates	ca. 470–399 B.C.	Executed by poison hemlock
Aristotle	384–322 B.C.	Described the preparation and use of arrow poisons
Theophrastus	ca. 370–286 B.C.	Referred to poisonous plants in *De Historia Plantarum*
Nicander	204–135 B.C.	Wrote two poems that are among the earliest works on poisons: *Theriaca* and *Alexipharmaca*
King Mithridates VI	ca. 132–63 B.C.	Fanatical fear of poisons; developed mithradatum, one of first universal antidotes
Cleopatra	69–30 B.C.	Committed suicide from deliberate cobra snake envenomation
Andromachus	A.D. 37–68	Refined the mithradatum; known as the Theriac of Andromachus
Dioscorides	A.D. 40–80	Wrote *Materia Medica*, which classified poison as animal, vegetable, or mineral
Galen	ca. A.D. 129–200	Prepared "Nut Theriac" for Roman emperors, a remedy against bites, stings, and poisons; wrote *De Antidots I* and *II*
Ibn Wahshiya	9th Century	Famed Arab toxicologist; wrote toxicology treatise *Book on Poisons*, combining contemporary science, magic, and astrology
Moses Maimonides	1135–1204	Wrote *Treatise on Poisons and Their Antidotes*
Paracelsus	1493–1541	Introduced dose-response concept to toxicology
Bernardino Ramazzini	1633–1714	Father of occupational medicine; wrote *De Morbis Artificum Diatriba*
Percivall Pott	1714–1788	First description of occupational cancer, relating the chimney sweep occupation to scrotal cancer
Felice Fontana	1730–1805	First scientific study of venomous snakes
Philip Physick	1767–1837	Early advocate of orogastric lavage to remove poisons
Edward Jukes	1820	Self-experimented with orogastric lavage apparatus known as Jukes' syringe
Grand Marshall Bertrand	1813	Demonstrated charcoal's efficacy in arsenic ingestion
Pierre Touery	1831	Demonstrated charcoal's efficacy in strychnine ingestion
Bonaventure Orfila	1787–1853	Father of modern toxicology; wrote Traite des Poisons; first to isolate arsenic from human organs
Claude Bernard	1813–1878	Studied mechanism of toxicity of carbon monoxide and curare
James Marsh	1794–1846	Developed reduction test for arsenic
Louis Lewin	1850–1929	Studied many toxins, including methanol, chloroform, snake venom, carbon monoxide, lead, opiates, and hallucinogenic plants
Alice Hamilton	1869–1970	Conducted landmark investigations associating worksite chemical hazards with disease; led reform movement to improve worker safety

full circle. Government-sanctioned execution in the United States again favored the use of a "state" poison: this time, the combination of sodium thiopental, pancuronium, and potassium chloride.

The use of a poison to achieve a political end resurfaced in December 2004 when it was announced that the Ukrainian presidential candidate Viktor Yushchenko was poisoned with the potent dioxin, TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin). The dramatic development of chloracne over the face of this public person during the previous several months suggested dioxin as a possible culprit. Given the paucity of reports of acute dioxin poisoning, however, it was not until laboratory tests confirmed that Yushchenko's dioxin levels were more than 6000 times normal that this remarkable diagnosis was confirmed. Table 1–2 lists other historically important figures in the history of toxicology and Table 1–3 identifies significant legislation in the United States involving poisons.

TABLE 1–2. Notable Poisoners from Antiquity to the Present

Poisoner	Date	Victim(s)	Poison(s)
Locusta	A.D. 54–55	Claudius and Britannicus	*Amanita phalloides*, cyanide
Cesare Borgia	1400s	Cardinals and kings	La Cantarella (arsenic and phosphorus)
Catherine de Medici	1519–1589	Poor, sick, criminals	Unknown agents
Madame Giulia Toffana	Died 1719	>600 people	Aqua toffana (arsenic trioxide)
Marchioness de Brinvilliers	Died 1676	Hospitalized patients, husband, father	Arsenic, lead, mercury, antimony, copper
Catherine Deshayes	Died 1680	>2000 infants, many husbands	La poudre de succession (arsenic mixed with aconite, belladonna, and opium)
Marie Lefarge	1839	Husband	Arsenic (first use of the Marsh test)
William Palmer, MD	1855	Fellow gambler	Strychnine
Edmond de la Pommerais, MD	1863	Patient and mistress	Digitalis
Edward William Pritchard, MD	1865	Wife and mother-in-law	Antimony
Adelaide Bartlett (acquitted)	1886	Husband	Chloroform
Florence Maybrick	1889	Husband	Arsenic
Thomas Neville Cream, MD	1891	Prostitutes	Strychnine
Hawley Harvey Crippen, MD	1910	Wife	Hyoscine
Nannie Doss	1954	11 relatives, including 5 husbands	Arsenic
Carl Coppolino, MD	1965	Wife	Succinylcholine
Graham Frederick Young	1971	Stepmother, coworkers	Thallium, antimony
Judias V. Buenoano	1971	Husband, son	Arsenic
Ronald Clark O'Bryan	1974	Son and neighborhood children	Cyanide (in Halloween candy)
Unknown	1978	Georgi Markov, Bulgarian defector	Ricin
Jim Jones	1978	911 people in mass suicide	Cyanide
Harold Shipman, MD	1974–1998	Patients (up to 297)	Heroin
George Trepal	1988	Neighbors	Thallium
Michael Swango, MD	1980s–1990s	Hospitalized patients	Succinylcholine, potassium chloride, arsenic
Charles Cullen, RN	1990s–2003	Hospitalized patients	Digoxin
Unknown	2004	Viktor Yushchenko, Ukrainian presidential candidate	Dioxin

TABLE 1–3. Protecting Our Health: Important US Regulatory Initiatives Pertaining to Xenobiotics Since 1900

Date	Federal Legislation	Intent
1906	Pure Food and Drug Act	Prohibits interstate commerce of misbranded and adulterated foods and drugs
1914	Harrison Narcotics Act	First federal law to criminalize the nonmedical use of drugs
1927	Federal Caustic Poison Act	Mandated labeling of concentrated caustics
1930	Food and Drug Administration (FDA) established	Successor to the Bureau of Chemistry; promulgation of food and drug regulations
1937	Marijuana Tax Act	Applied controls to marijuana similar to those applied to narcotics
1938	Federal Food, Drug, and Cosmetic Act	Required toxicity testing of pharmaceuticals prior to marketing
1948	Federal Insecticide, Fungicide, and Rodenticide Act	Provided federal control for pesticide sale, distribution, and use
1960	Federal Hazardous Substances Labeling Act	Mandated prominent labeling warnings on hazardous household chemical products
1962	Kefauver-Harris Drug Amendments	Required drug manufacturer to demonstrate efficacy before marketing
1963	Clean Air Act	Regulated air emissions by setting maximum pollutant standards
1966	Child Protection Act	Banned hazardous toys when adequate label warnings could not be written
1970	Environmental Protection Agency (EPA) established	Established and enforced environmental protection standards
1970	Occupational Safety and Health Act (OSHA)	Created National Institute for Occupational Safety and Health (NIOSH) as research institution for OSHA
1970	Poison Prevention Packaging Act	Mandated child-resistant safety caps on certain pharmaceutical preparations
1972	Clean Water Act	Regulated discharge of pollutants into US waters
1972	Consumer Product Safety Act	Established Consumer Product Safety Commission
1972	Hazardous Material Transportation Act	Authorized the Department of Transportation to regulate for the safe transportation of hazardous materials
1973	Drug Enforcement Administration (DEA) created	Succeeded predecessor Bureau of Narcotics and Dangerous Drugs; charged with enforcing federal drug laws
1973	Lead-based Paint Poison Prevention Act	Regulated the use of lead in residential paint. Lead in some paints later banned by Congress in 1978
1974	Safe Drinking Water Act	Set safe standards for water purity

1976	Resource Conservation and Recovery Act (RCRA)	Authorized EPA to control hazardous waste from its generation to its disposal
1976	Toxic Substance Control Act	Authorized EPA to track 75,000 industrial chemicals produced or imported into the United States
1980	Comprehensive Environmental Response Compensation and Liability Act (CERCLA)	Established trust fund (Superfund) to provide cleanup for hazardous waste sites. Agency for Toxic Substances and Disease Registry (ATSDR) created
1983	Federal Anti-Tampering Act	Response to cyanide-Tylenol deaths. Outlawed tampering with packaged consumer products
1986	Controlled Substance Analogue Enforcement Act	Instituted legal controls on analog (designer) drugs with chemical structures similar to controlled substances
1986	Drug-Free Federal Workplace Program	Executive order mandating drug testing of federal employees in sensitive positions
1986	Superfund Amendments and Reauthorization Act (SARA)	Amendment to CERCLA. Increased funding for hazardous waste (SARA) sites
1994	Dietary Supplement Health and Education Act	Permitted dietary supplements including many herbal preparations to bypass FDA scrutiny
1997	FDA Modernization Act	Accelerated FDA reviews, regulated advertising of unapproved uses of approved drugs
2002	The Public Health Security and Bioterrorism Preparedness and Response Act	Tightened control on biologic agents and toxins; increased safety of the US food and drug supply, and drinking water; and strengthened the Strategic National Stockpile

Antiquated Antidotes

Although the judicious use of some antidotes (eg, *N*-acetylcysteine, naloxone, pyridoxine) is critically important in the management of select poisoned patients, other antidotes do not necessarily offer a distinct clinical advantage and may create additional problems (eg, flumazenil, physostigmine), and others have been found to be outmoded or antiquated.

ANALEPTICS

Analeptics are nonspecific arousal xenobiotics and include such stimulants as strychnine, camphor, caffeine, picrotoxin, pentylenetetrazol, nikethamide, amphetamine, and methylphenidate. The principal goal of analeptic therapy was to awaken the patient as soon as possible. Many of these xenobiotics function to reduce γ-aminobutyric acid (GABA)-mediated inhibitory tone.

Unfortunately, many adverse effects occurred with the use of analeptics, including hyperthermia, dysrhythmias, seizures, and psychoses. It gradually became evident that analeptic therapy, despite its theoretic benefits, offered no real advantage, did not reduce mortality, and placed the patient at risk for significant iatrogenic complications.

Beginning in the mid-1940s, a distinctive approach to barbiturate overdose was pioneered by Eric Nilsson and Carl Clemmesen at the Bispebjerg Hospital, Copenhagen, Denmark. This treatment regimen, known as the *Scandinavian method*, abandoned the use of analeptics in the treatment of barbiturate overdoses. Instead of primarily emphasizing the termination of coma, attention was directed at intensive supportive therapy with respiratory ventilation, oxygenation, and cardiovascular support. This strategy was analogous to the postanesthetic recovery room care provided to surgical patients. Using this "revolutionary" approach, barbiturate overdose mortality significantly dropped from approximately 20% with stimulation therapy to 1–2% with the Scandinavian method.

EARLY TREATMENTS OF OPIOID OVERDOSES

Prior to the 1950s, opioid overdose was treated with many of the same analeptics. In the early 1950s, two specific opioid antidotes were introduced: nalorphine (Nalline) and levallorphan (Lorfan). These drugs reversed the respiratory effects of an opioid overdose by blocking opioid receptors. Unfortunately, nalorphine and levallorphan were mixed agonist/antagonists rather than pure antagonists, limiting their usefulness. Respiratory depression could be potentiated, especially in opioid-free patients. This was most likely to occur when these drugs were administered to comatose patients with mild hypoventilation who had overdosed on sedative-hypnotics or ethanol. Naloxone, introduced in the 1970s, is a pure opioid antagonist and has replaced these other opioid-reversal agents.

DISCARDED TREATMENTS FOR ETHANOL WITHDRAWAL

In the mid-19th century, opium and, later, morphine were the primary pharmacologic treatments for severe ethanol withdrawal. Unfortunately, this ap-

proach was associated with problems related to opioid toxicity in these unmonitored patients. Adjuncts used with the opioids included digitalis, which was thought to provide benefit to counteract the adverse cardiac effects associated with ethanol withdrawal. Once introduced, drugs such as ether and chloroform were inhalationally administered to induce sleep for up to 24 hours. Other drugs that were employed included the bromide salts, but they proved difficult to use and, in some cases, were associated with the development of bromism.

By the early 20th century, chloral hydrate, barbiturates, and paraldehyde also became mainstays of ethanol withdrawal therapy. Although some patients responded well to paraldehyde, it proved very difficult to titrate because of its variable rates of absorption. Additionally, it was associated with the development of metabolic acidosis. Ethanol administered either intravenously or orally also has been used to suppress withdrawal. However, its very short duration of action, its titration difficulties, and its CNS metabolic effects and hepatotoxicity make it a suboptimal choice.

OUTDATED AND DANGEROUS EMETICS

Tartar emetic, an antimony salt, had a long history of use as an emetic, as well as a sedative, expectorant, cathartic, and diaphoretic, but it is no longer used because of its toxicity. The use of saltwater emetics was abandoned after numerous cases of severe salt poisoning resulted from their administration. Mustard powder has never proven effective. The use of copper sulfate as an emetic also fell out of favor because of its caustic properties, its potential to cause acute copper poisoning, and its unreliability. Zinc sulfate also is no longer used as an emetic.

Until the 1980s, apomorphine was advocated as an emetic. It had a rapid onset of action but its propensity to cause CNS depression increased the risk of subsequent aspiration and made its use potentially very dangerous.

THE UNIVERSAL ANTIDOTE

For many years the "universal antidote," sold under the trade names Unidote and Res-Q, was a medical tradition and was advocated by many textbooks as part of the standard management of the poisoned patient. Commercial preparations consisted of 1 part magnesium oxide, 1 part tannic acid, and 2 parts activated charcoal. An alternative home recipe consisted of milk of magnesia, strong tea, and burnt toast. Combination therapy of this sort was thought to offer a broader spectrum of action than activated charcoal alone. It was theorized that the magnesium oxide would neutralize acids and the tannic acid would precipitate alkaloids and metals. Studies demonstrated that activated charcoal was superior to the universal antidote in decreasing absorption and that the decreased efficacy of the universal antidote was caused by tannic acid interfering with activated charcoal's adsorption of other toxins.

OTHER ANTIQUATED ANTIDOTES

Until the 1970s, typical recommendations for the treatment of alkali ingestions included the use of vinegar (acetic acid), lemon juice, or, in some cases, dilute hydrochloric acid. Suggestions for neutralizing acid ingestions included the use of magnesium hydroxide, lime water, and calcium carbonate.

Because of the extremely rapid onset of action of caustics, concerns arose over whether it was already too late to reverse the caustic process. Furthermore, the addition of neutralizing agents could increase the potential for a consequential exothermic reaction and/or gas production. Such reactions in an already weakened hollow viscus may be poorly tolerated and lead to extension of the tissue injury or perforation. For all of these reasons, the use of neutralizing agents is no longer recommended.

Other antiquated antidotes include ferric hydroxide (*antidotum arsenici*), which was used in the treatment of arsenic poisoning. Acetazolamide, which was advocated for alkalinizing the urine in salicylate poisoning, causes a metabolic acidemia that can worsen the salicylate toxicity, and, consequently, is no longer used. The use of sodium phosphate (Phospho-Soda) in the management of iron overdose in an attempt to create insoluble ferrous phosphate also has ceased because of problems with its marginal efficacy and resultant hyperphosphatemia.

Many of our current antidotes have not undergone rigorous scientific evaluation regarding efficacy and safety. In time, some of these antidotes will undoubtedly join this list of antiquated antidotes. Lessons learned from the past, such as the abandonment of analeptics, help to optimize present-day patient care and to better prepare us to investigate and evaluate the next generation of antidotes.

2 Toxicologic Plagues and Disasters in History

Throughout history, mass poisonings have caused suffering and misfortune. From the ergot epidemics of the Middle Ages to contemporary industrial disasters, these plagues have had great political, economic, social, and environmental ramifications. Particularly within the last 100 years, as the number of toxins and potential toxins has risen dramatically, toxic disasters are an increasingly common event. The sites of some of these events—Bhopal (India), Chernobyl (Ukraine), Love Canal (New York), Minamata Bay (Japan), Seveso (Italy), West Bengal (India)—have come to symbolize our increasingly toxic habitat. This chapter is an overview of some of the most consequential and historically important toxin-associated disasters. Globalization has led to the proliferation of toxic chemicals throughout the world. Many chemical factories are not secure despite their storage of large amounts of potentially lethal chemicals. Given the increasing attention to terrorism preparedness, an appreciation of chemicals as agents of opportunity for terrorists to employ as weapons has suddenly assumed much greater importance.

GAS DISASTERS

Inhalation of toxic gases and oral ingestions resulting in food poisoning tend to subject the greatest number of people to adverse consequences of a toxic exposure (Table 2–1). Toxic gas exposures may be the result of a natural disaster (volcanic eruption), industrial mishap (fire, chemical release), chemical warfare, or intentional homicidal or genocidal endeavor (concentration camp gas chamber). Depending on the toxin, the clinical presentation may be acute, with a rapid onset of toxicity (cyanide), or subacute/chronic, with a gradual onset of toxicity (air pollution).

WARFARE AND TERRORISM

Exposure to toxic chemicals with the deliberate intent to inflict harm claimed an extraordinary number of victims during the 20th century (Table 2–2).

During recent wars and terrorism events, a variety of physical and neuropsychological ailments have been attributed to possible exposure to toxic agents. Gulf War syndrome is a constellation of chronic symptoms, including fatigue, headache, muscle and joint pains, ataxia, paresthesias, diarrhea, skin rashes, sleep disturbances, impaired concentration, memory loss, and irritability, which were noted in thousands of Persian Gulf War veterans without a clearly identifiable cause. A number of etiologies have been advanced to explain these varied symptoms, including exposure to the smoke from burning oil wells; chemical and biological warfare agents, including nerve agents; and medical prophylaxis, such as the use of pyridostigmine bromide, anthrax vaccine, and botulinum toxin vaccine, although the actual etiology remains unclear.

TABLE 2–1. Gas Disasters

Toxin	Location	Date	Significance
Smog (SO_2)	London	1873	268 deaths from bronchitis
NO_2, CO, CN	Cleveland Clinic	1929	Fire in radiology department, 125 deaths
Smog (SO_2)	Belgium, Meuse Valley	1930	64 deaths
CO, CN	Cocoanut Grove Night Club, Boston, MA	1942	498 deaths from fire
CO	Salerno, Italy	1944	>500 deaths on train stalled in tunnel
Smog (SO_2)	Donora, PA	1948	20 deaths, thousands ill
Smog (SO_2)	London	1952	4000 deaths
Dioxin	Seveso, Italy	1976	Unintentional industrial release of dioxin into environment; chloracne
Methyl isocyanate	Bhopal, India	1984	>2000 deaths; 200,000 injuries
CO_2	Cameroon	1986	>1700 deaths from release of gas from Lake Nyos
CO, ?CN	Happy Land Social Club, Bronx, NY	1990	87 died in fire from toxic smoke
Hydrogen sulfide	Xiaoying, China	2003	243 died and 10,000 became ill from gas poisoning after a gas well exploded
CO, ?CN	West Warwick, RI	2003	98 died in fire

TABLE 2–2. Warfare and Terrorism Disasters

Toxin	Location	Date	Significance
Chlorine, phosgene, mustard gas	Ypres, Belgium	1915–1918	100,000 dead/1.2 million casualties from chemicals during World War I
CN, CO	Europe	1939–1945	Millions murdered by Zyklon-B (HCN) gas
Agent Orange	Vietnam	1960s	Contained dioxin
Mustard gas	Iraq-Iran	1982	New cycle of war gas casualties
Toxic smoke?	Persian Gulf	1991	Gulf War syndrome—possible toxic etiology
Sarin	Matsumoto, Japan	1994	First of terrorist attacks in Japan using sarin
Sarin	Tokyo	1995	Subway exposure; 5510 people seek medical attention
Dust and other particulates	New York, NY	2001	World Trade Center collapse from terrorist air strike resulted in significant respiratory disease among rescuers

FOOD DISASTERS

Unintentional contamination of food and drink has led to numerous toxic disasters (Table 2–3). Poisoning may occur as a consequence of the introduction of a multitude of xenobiotics in the food supply at the level of the end user or earlier in the food supply chain. Although most of these epidemics were unintentional, some were not, and nearly all were preventable.

TABLE 2–3. Food Disasters

Toxin	Location	Date	Significance
Ergot	Aquitania, France	A.D. 994	40,000 died in the epidemic
Ergot	Salem, MA	1692	Neuropsychiatric symptoms may be attributable to ergot
Lead	Devonshire, England	1700s	Colic from production of cider
Arsenious acid	France	1828	40,000 cases of polyneuropathy from contaminated wine and bread
Lead	Canada	1846	134 men died during the Franklin expedition, possibly because of contamination of food stored in lead cans
Arsenic	Staffordshire, England	1900	Arsenic-contaminated sugar used in beer production
Cadmium	Japan	1939–1954	Itai-itai ("ouch-ouch") disease
Hexachlorobenzene	Turkey	1956	4000 cases of porphyria cutanea tarda
Methyl mercury	Minamata Bay, Japan	1950s	Organic mercury poisoning from fish
Triorthocresyl phosphate	Meknes, Morocco	1959	Cooking oil adulterated with turbojet lubricant
Cobalt	Quebec City, Canada, and others	1960s	Cobalt beer cardiomyopathy
Methylenedianiline	Epping, England	1965	Jaundice
Polychlorinated biphenyls	Japan	1968	Yusho disease
Methyl mercury	Iraq	1971	>400 deaths from contaminated grain
Polybrominated biphenyls	Michigan	1973	97% of state contaminated through food chain
Polychlorinated biphenyls	Taiwan	1979	Yu-Cheng disease
Rape seed oil (denatured)	Spain	1981	Toxic oil syndrome affected 19,000 people
Arsenic	Buenos Aires	1987	Malicious contamination of meat; 61 people underwent chelation
Arsenic	Bangladesh and West Bengal, India	1990s–present	Ground water contaminated with arsenic; millions exposed; 100,000s with symptoms; greatest mass poisoning in history
Nicotine	Michigan	2003	Deliberate contamination of ground beef; 92 people became ill

MEDICINAL DRUG DISASTERS

Illness and death as a consequence of therapeutic drug use occur as sporadic events, usually affecting individual patients, or as mass disasters, affecting multiple (sometimes hundreds or thousands) patients. Sporadic single-patient medication-induced tragedies usually result from errors or unforeseen idiosyncratic reactions. Mass therapeutic drug disasters have generally occurred secondary to poor safety testing, a lack of understanding of diluents and excipients, drug contamination, or problems with unanticipated drug–drug interactions or drug toxicity (Table 2–4).

ALCOHOL AND ILLICIT DRUG DISASTERS

Unintended toxic disasters have also resulted from the contamination or adulteration of alcohol and other drugs of abuse (Table 2–5).

OCCUPATIONAL-RELATED CHEMICAL DISASTERS

Unfortunately, occupational toxic epidemics are increasingly common (Table 2–6). These poisoning syndromes tend to have an insidious onset and may not be recognized clinically until years after the exposure. A specific toxin may cause myriad problems, among the most worrisome being the toxin's carcinogenic and mutagenic potentials. While the observations of Ramazzini and Pott in the 18th century introduced the concept that certain diseases were a direct result of toxic exposures in the workplace, it was not until the height of the 19th century's industrial revolution that the problems associated with the increasingly hazardous workplace became apparent.

TABLE 2–4. Medicinal Disasters

Toxin	Location	Date	Significance
Thallium	US	1920s–1930s	Used for ringworm; 31 deaths
Diethylene glycol	US	1937	Elixir of sulfanilamide; renal failure and death
Thorotrast	US	1930s–1950s	Hepatic angiosarcoma
Phenobarbital	US	1940–1941	Sulfathiazole contaminated with phenobarbital; 82 deaths
Diethylstilbestrol (DES)	US, Europe	1940s–1970s	Vaginal adenocarcinoma in daughters
Stalinon	France	1954	Severe neurotoxicity from triethyltin
Thalidomide	Europe	1960s	5000 cases of phocomelia
Isoproterenol 30%	Great Britain	1961–1967	3000 excess asthma deaths
Pentachlorophenol	US	1967	Used in hospital laundry; 9 neonates ill, 2 deaths
Benzyl alcohol	US	1981	Gasping syndrome
Acetaminophen-cyanide	Chicago	1982	Tampering incident resulted in 7 homicides
L-Tryptophan	US	1989	Eosinophilia-myalgia syndrome
Diethylene glycol	Haiti	1996	Acetaminophen elixir contaminated; renal failure; >88 pediatric deaths

TABLE 2–5. Alcohol and Illicit Drug Disasters

Toxin	Location	Date	Significance
Triorthocresyl phosphate	US	1930–1931	Ginger Jake paralysis
Methanol	Atlanta, GA	1951	Epidemic from ingesting bootleg whiskey
Methanol	Jackson, MI	1979	Occurred in a prison
MPTP	San Jose, CA	1982	Illicit meperidine manufacturing resulting in drug-induced parkinsonism
3-Methyl fentanyl	Pittsburgh, PA	1988	"China-white" epidemic
Methanol	Baroda, India	1989	Moonshine contamination; 100 deaths
Fentanyl	New York, NY	1990	"Tango and Cash" epidemic
Methanol	New Delhi, India	1991	Antidiarrheal medication contaminated with methanol; >200 deaths
Methanol	Cuttack, India	1992	Methanol tainted liquor; 162 deaths
Scopolamine	US East Coast	1995–1996	325 cases of anticholinergic poisoning in heroin users
Methanol	Cambodia	1998	>60 deaths

TABLE 2–6. Occupational Disasters

Toxin	Location	Date	Significance
Polycyclic aromatic hydrocarbons	England	1700s	High incidence of scrotal cancer among chimney sweeps; first description of occupational cancer
Mercury	New Jersey	Mid- to late 1800s	Outbreak of mercurialism in hatters
White phosphorus	Europe	Mid- to late 1800s	Phossy-jaw in matchmakers
β-Naphthylamine	Worldwide	Early 1900s	Increased bladder cancer in dye makers
Benzene	Newark, NJ	1916–1928	Aplastic anemia among artificial leather manufacturers
Asbestos	Worldwide	20th century	Millions at risk for asbestos-related disease
Vinyl chloride	Louisville, KY	1960s–1970s	Increased cases of hepatic angiosarcoma among polyvinyl chloride polymerization workers
Chlordecone	James River, VA	1973–1975	Increased incidence of neurologic abnormalities among insecticide workers
1,2-Dibromochloropropane	California	1974	Infertility among pesticide makers

RADIATION DISASTERS

A discussion of mass poisonings is incomplete without mention of a growing number of radiation disasters that have occurred in the 20th century (Table 2–7).

TABLE 2–7. Radiation Disasters

Toxin	Location	Date	Significance
Radium	Orange, NJ	1910s–1920s	Increase in bone cancer in dial-painting workers
Radium	US	1920s	"Radithor" (radioactive water) sold as radium-containing patent medication
Radiation	Hiroshima and Nagasaki, Japan	1945	First atomic bombs dropped at end of World War II; clinical effects still evident today
Radiation	Chernobyl, USSR	1986	Human error produced an explosion that scattered radiation throughout Europe and beyond
Cesium	Goiania, Brazil	1987	Acute radiation sickness and radiation burns

PART A THE GENERAL APPROACH TO MEDICAL TOXICOLOGY

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3 Initial Evaluation of the Patient: Vital Signs and Toxic Syndromes

For more than 200 years the American medical community has attempted to standardize its approach to the assessment of patients. In the practice of medical toxicology, vital signs play an important role beyond assessing and monitoring the overall status of a patient, as they frequently provide valuable physiologic clues to the toxicologic etiology and severity of an illness. The vital signs also are a valuable parameter with which to assess and monitor a patient's response to supportive treatment and antidotal therapy.

Table 3–1 presents the normal vital signs for various age groups. However, the broad range of values considered normal should serve merely as a guide. Only the complete assessment of a patient can determine whether or not a particular vital sign is truly clinically normal. This table of normal vital signs is useful in assessing children, as normal values for children vary considerably with age, and knowing the range of variation is essential. The normal temperature is defined as 95–100.4°F (35–38°C).

Table 3–2 describes the most typical toxic syndromes. This table includes only those vital signs that are thought to be characteristically abnormal or pathognomonic and directly related to the toxicologic effect of the xenobiotic. The main purpose of the table, however, is to include the many findings in addition to the vital signs that together constitute a toxic syndrome. Mofenson and Greensher coined the term *toxidrome* from the words *toxic syndrome* to describe the groups of signs and symptoms that consistently result from particular toxins. These syndromes are usually best described by a combination of the vital signs and clinically obvious end-organ manifestations. The signs that prove most clinically useful are those involving the central nervous system (mental status); ophthalmic system (pupil size); gastrointestinal system (peristalsis); dermatologic system: skin (dryness vs. diaphoresis) and mucous membranes (moistness vs. dryness); and genitourinary system (urinary retention vs. incontinence). Table 3–3 includes some of the most important signs and symptoms and the xenobiotics most commonly responsible for these manifestations. A detailed analysis of each sign, symptom, and toxic syndrome can be found in the pertinent chapters throughout this text.

In considering a toxic syndrome, the reader should always remember that the actual clinical manifestations of an ingestion or exposure are far more variable than the syndromes described in Table 3–2. Although some patients may present as "classic" cases, others will manifest partial toxic syndromes or *formes frustes.* Incomplete syndromes still may provide at least a clue to the correct diagnosis. It is important to understand that partial presentations (particularly in the presence of multiple xenobiotics) do not necessarily imply less severe disease and, therefore, are no less important to appreciate.

Tables 3–4 to 3–7 highlight xenobiotics commonly associated with various vital sign abnormalities.

TABLE 3–1. Normal Vital Signs by Age

Age	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats/min)	Respirations (breaths/min)*
Adult	120	80	60–100	16–24
16 years	120	80	80	16–30
12 years	119	76	85	16–30
10 years	115	74	90	16–30
6 years	107	69	100	20–30
4 years	104	65	110	20–30
2 years	102	58	120	25–30
1 year	100	55	120	25–30
6 months	90	55	120	30
4 months	90	50	145	30–35
2 months	85	50	145	30–35
Newborn	65	50	145	35–40

The normal rectal temperature is defined as 95–100.4°F (35–38°C) for all ages. For children ≤1 year of age these values are the mean values for the 50th percentile. For the older children these values represent the 90th percentile at a specific age for the 50th percentile of weight in that age group.
*These values were determined in the emergency department and may be environment and situation dependent.

TABLE 3–2. Toxic Syndromes

Group	Vital Signs BP	P	R	T	Mental Status	Pupil Size	Peristalsis	Diaphoresis	Other
Anticholinergics	–/↑	↑	±	↑	Delirium	↑	↓	↓	Dry mucous membranes, flush, urinary retention
Cholinergics	±	±	–/↑	–	Normal to depressed	±	↑	↑	Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative-hypnotics	↓	↓	↓	–/↓	Depressed	±	↓	–	Hyporeflexia, ataxia
Opioids	↓	↓	↓	↓	Depressed	↓	↓	–	Hyporeflexia
Sympathomimetics	↑	↑	↑	↑	Agitated	↑	–/↑	↑	Tremor, seizures
Withdrawal from ethanol or sedative-hypnotics	↑	↑	↑	↑	Agitated, disoriented	↑	↑	↑	Tremor, seizures
Withdrawal from opioids	↑	↑	–	–	Normal, anxious	↑	↑	↑	Vomiting, rhinorrhea, piloerection, diarrhea, yawning

↑ = increases; ↓ = decreases; ± = variable; – = change unlikely.

TABLE 3–3. Clinical and/or Laboratory Findings in Poisoning

Agitation	Anticholinergics[a], hypoglycemia, phencyclidine, sympathomimetics[b], withdrawal from ethanol and sedative-hypnotics
Alopecia	Alkylating agents, radiation, selenium, thallium
Ataxia	Benzodiazepines, carbamazepine, carbon monoxide, ethanol, hypoglycemia, lithium, mercury, nitrous oxide, phenytoin
Blindness or decreased visual acuity	Caustics (direct), cocaine, cisplatin, mercury, methanol, quinine, thallium
Blue skin	Amiodarone, FD&C #1 dye, methemoglobin, silver
Constipation	Anticholinergics[a], botulism, lead, opioids, thallium (severe)
Tinnitus, deafness	Aminoglycosides, cisplatin, metals, loop diuretics, quinine, salicylates
Diaphoresis	Amphetamines, cholinergics[c], hypoglycemia, opioid withdrawal, salicylates, serotonin syndrome, sympathomimetics[b], withdrawal from ethanol and sedative-hypnotics
Diarrhea	Arsenic and other metals, boric acid (blue-green), botanical irritants, cathartics, cholinergics[c], colchicine, iron, lithium, opioid withdrawal, radiation
Dysesthesias, paresthesias	Acrylamide, arsenic, ciguatera, cocaine, colchicine, thallium
Gum discoloration	Arsenic, bismuth, hypervitaminosis A, lead, mercury
Hallucinations	Anticholinergics[a], dopamine agonists, ergot alkaloids, ethanol, ethanol and sedative-hypnotic withdrawal, LSD, phencyclidine, sympathomimetics[b], tryptamines (eg, AMT)
Headache	Carbon monoxide, hypoglycemia, monoamine oxidase inhibitor/food interaction (hypertensive crisis), serotonin syndrome
Metabolic acidosis (elevated anion gap) [MUDPILES]	Methanol, uremia, ketoacidosis (diabetic, starvation, alcoholic), paraldehyde, phenformin, metformin, iron, isoniazid, lactic acidosis, cyanide, protease inhibitors, ethylene glycol, salicylates, toluene
Miosis	Cholinergics[c], clonidine, opioids, phencyclidine, phenothiazines
Mydriasis	Anticholinergics[a], botulism, opioid withdrawal, sympathomimetics[b]
Nystagmus	Barbiturates, carbamazepine, carbon monoxide, ethanol, lithium, monoamine oxidase inhibitors, phencyclidine, phenytoin, quinine
Purpura	Anticoagulant rodenticides, clopidogrel, corticosteroids, heparin, pit viper venom, quinine, salicylates, warfarin
Radiopaque ingestions	Arsenic, chloral hydrate, enteric coated tablets, halogenated hydrocarbons, metals (eg, iron, lead)
Red skin	Anticholinergics[a], boric acid, disulfiram, scombroid, vancomycin
Rhabdomyolysis	Carbon monoxide, doxylamine, HMG CoA reductase inhibitors, sympathomimetics[b], *Tricholoma equestre*
Salivation	Arsenic, caustics, cholinergics[c], ketamine, mercury, phencyclidine, strychnine, clozaphine
Seizures	Bupropion, carbon monoxide, cyclic antidepressants, *Gyromitra* mushrooms, hypoglycemia, isoniazid, methylxanthines, withdrawal from ethanol and sedative-hypnotics
Tremor	Antipsychotics, arsenic, carbon monoxide, cholinergics[c], ethanol, lithium, mercury, methyl bromide, sympathomimetics[b], thyroid replacement

(continued)

TABLE 3–3. Clinical and/or Laboratory Findings in Poisoning *(continued)*

Weakness	Botulism, diuretics, magnesium, paralytic shellfish, steroids, toluene
Yellow skin	Acetaminophen (late), pyrrolizidine alkaloids, β carotene, amatoxin mushrooms. dinitrophenol

[a]Anticholinergics: eg, antihistamines, atropine, cyclic antidepressants, scopolamine.
[b]Sympathomimetics: eg, amphetamines, β adrenergic agonists, cocaine, ephedrine.
[c]Cholinergics: eg, muscarinic mushrooms, organic phosphorus compounds and carbamates including select Alzheimer drugs and physostigmine, pilocarpine and other direct acting drugs.

TABLE 3–4. Common Xenobiotics That Affect Blood Pressure

Hypotension	Hypertension
α_1-Adrenergic antagonists	Ergot alkaloids
α_2-Adrenergic agonists	Lead (chronic)
β-Adrenergic antagonists	Monoamine oxidase inhibitors
Angiotensin converting enzyme inhibitors and angiotensin receptor blockers	(overdose early and drug–food interaction)
Antidysrhythmics	Nicotine (early)
Calcium channel blockers	Phencyclidine
Cyanide	Sympathomimetics
Cyclic antidepressants	Yohimbine
Ethanol and other alcohols	
Iron	
Methylxanthines	
Nitrates and nitrites	
Nitroprusside	
Opioids	
Phenothiazines	
Phosphodiesterase-5′ inhibitors	
Sedative-hypnotics	

Chap. 23 lists additional agents that affect hemodynamic function.

TABLE 3–5. Common Xenobiotics That Affect Pulse

Bradycardia	Tachycardia
α_2-Adrenergic agonists	Anticholinergics
β-Adrenergic antagonists	Cyclic antidepressants
Baclofen	Disulfiram/ethanol
Calcium channel blockers	Ethanol and sedative hypnotic withdrawal
Cardioactive steroids	Iron
Ciguatera	Methylxanthines
Ergot alkaloids	Phencyclidine
Opioids	Phenothiazines
	Sympathomimetics
	Thyroid replacement
	Yohimbine

Chap. 23 lists additional agents affecting heart rate.

TABLE 3–6. Common Xenobiotics That Affect Respiration

Bradypnea	Tachypnea
α_2-Adrenergic agonists	Cyanide
Botulinum toxin	Dinitrophenol and congeners
Ethanol and other alcohols	Epinephrine
γ-Hydroxybutyric acid	Ethylene glycol
Neuromuscular blockers	Hydrogen sulfide
Opioids	Methanol
Organic phosphorus insecticides	Methemoglobin producers
Sedative-hypnotics	Methylxanthines
	Nicotine (early)
	Salicylates
	Sympathomimetics

Chap. 22 lists additional agents affecting respiratory rate.

TABLE 3–7. Common Xenobiotics That Affect Temperature

Hyperthermia	Hypothermia
Anticholinergics	α_2-Adrenergic agonists
Chlorphenoxy herbicides	Carbon monoxide
Dinitrophenol and congeners	Ethanol
Malignant hyperthermia	Hypoglycemic agents
Monoamine oxidase inhibitors	Opioids
Neuroleptic malignant syndrome	Sedative-hypnotics
Phencyclidine	Thiamine deficiency
Salicylates	
Sedative-hypnotic or ethanol withdrawal	
Serotonin syndrome	
Sympathomimetics	
Thyroid replacement	

Chap. 16 lists additional agents affecting temperature.

4 Principles of Managing the Poisoned or Overdosed Patient

Medical toxicologists and poison information specialists typically use a clinical approach to the poisoned patient that emphasizes treating the patient rather than treating the poison. Too often in the past, patients were initially all but neglected while attention was focused on the ingredients listed on the containers of the product(s) to which, presumably, they were exposed. Although the astute clinician must always be prepared to administer a specific antidote immediately in those instances when nothing else will save a patient, all poisoned or overdosed patients will benefit from an organized, rapid clinical management plan (Fig. 4–1).

In the mid-1970s, most medical toxicologists began to advocate a standardized approach to a comatose and possibly overdosed adult patient, typically calling for the intravenous administration of 50 mL of $D_{50}W$, 100 mg of thiamine, 2 mg of naloxone, as well as 100% oxygen at high flow rates. Today, however, with the widespread availability of accurate, rapid reagent, bedside testing for blood glucose and pulse oximetry for oxygen saturation, coupled with a greater appreciation of individualized care for the overdose patient, clinicians can safely provide a more rational approach that calls for selective use of these therapies.

A second major approach to providing more rational individualized early treatment for toxicologic emergencies involves a closer examination of the actual benefits and risks of various gastrointestinal decontamination techniques. Appreciation of the potential for significant adverse effects associated with all types of gastrointestinal decontamination techniques and recognition of the absence of clear evidence-based support of efficacy, have led to a significant reduction in the routine use of syrup of ipecac-induced emesis and orogastric lavage, as well as cathartic-induced intestinal evacuation. Additionally, the value of whole bowel irrigation with polyethylene glycol electrolyte solution [whole-bowel irrigation (WBI) with polyethylene glycol electrolyte lavage solution (PEG-ELS)] appears to be much more specific and limited than originally thought. Likewise, some of the limitations and (uncommon) adverse effects of activated charcoal (AC) are now more widely recognized.

Similarly, interventions to eliminate absorbed toxins from the body are now much more narrowly defined or, in some cases, abandoned: Multiple-dose activated charcoal (MDAC) is useful for only a few xenobiotics. Ion-trapping in the urine is only beneficial, achievable, and relatively safe when the urine can be maximally alkalinized after a significant salicylate, phenobarbital, or chlorpropamide poisoning. Finally, the roles of hemodialysis, hemoperfusion, and other extracorporeal techniques are now much more specifically defined.

INITIAL MANAGEMENT OF A PATIENT WITH A SUSPECTED TOXIC EXPOSURE

The clinical approach to potentially poisoned patients begins with the recognition and treatment of life-threatening conditions: airway compromise, breathing difficulties, and circulatory problems (the "ABCs") such as hemodynamic instability and serious dysrhythmias. Once the ABCs are addressed,

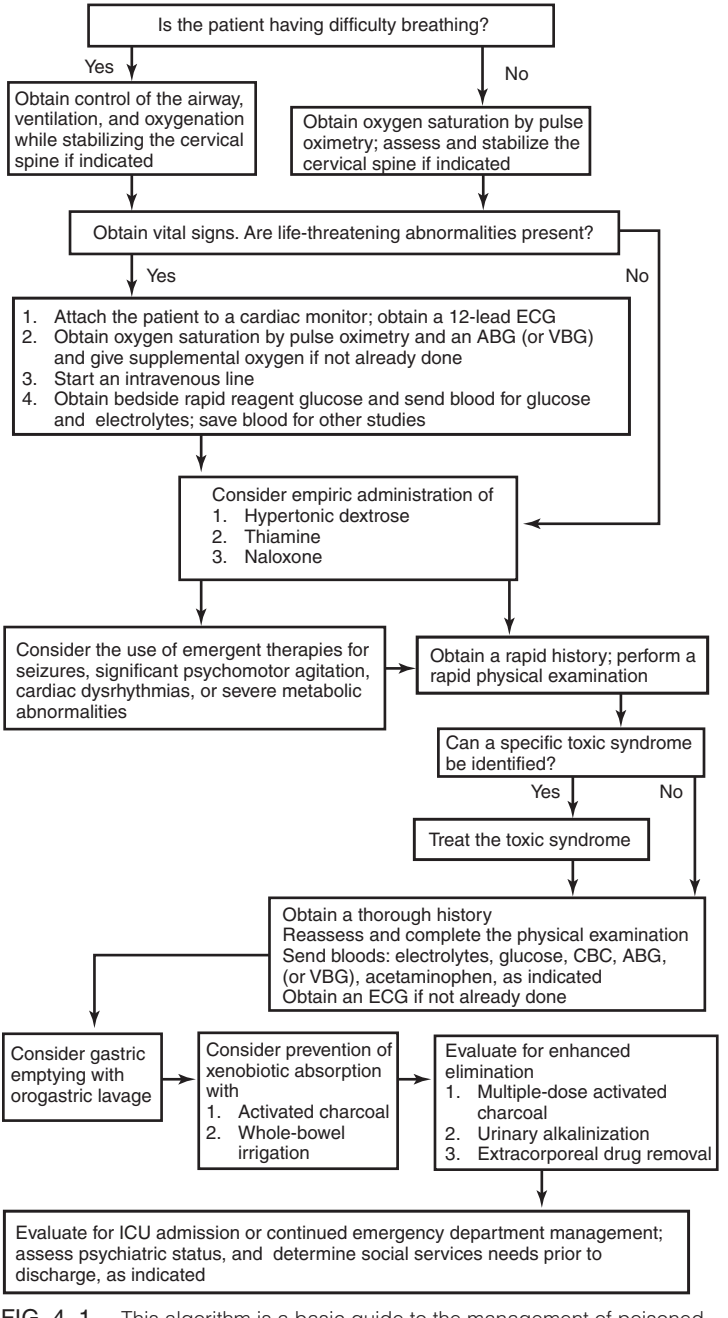


FIG. 4–1. This algorithm is a basic guide to the management of poisoned patients. A more detailed description of the steps in management may be found in the accompanying text. This algorithm is only a guide to actual management, which must, of course, consider the patient's clinical status.

the patient's level of consciousness should be assessed, as this helps to determine the techniques to be used for further management of the exposure. Extremes of core body temperature must be addressed early in the evaluation and treatment of a patient with altered mental status.

In most cases, a bedside, rapid reagent, blood glucose determination should be obtained as soon as possible, followed by an ECG. Both of these rapid, inexpensive, minimally invasive tests provide essential clues to the life-threatening problems of hypoglycemia and cardiotoxicity, respectively. Continuous electrocardiographic monitoring should be instituted until the clinician is certain that the patient is stable. For the hypotensive patient with clear lungs and an unknown overdose, a fluid challenge with intravenous 0.9% NaCl or lactated Ringer solution may be started. If the patient remains hypotensive or cannot tolerate fluids, a vasopressor or an inotrope might be indicated, as well as more invasive monitoring.

At the time that the IV catheter is inserted, blood samples for glucose, electrolytes, BUN, a complete blood count (CBC), and any indicated toxicologic analysis can be drawn. Indiscriminate toxicology screening of either the blood or urine rarely provides clinically useful information. However, for the potentially suicidal patient, an acetaminophen serum concentration should be routinely requested. In the vast majority of cases, the blood tests that are most useful in diagnosing toxicologic emergencies are not the "toxicologic" assays but the "nontoxicologic" routine metabolic profile tests such as BUN, glucose, electrolytes, and arterial blood gases (ABGs) or venous blood gases (VBGs).

Within the first 5 minutes of managing a patient with an altered mental status, four therapeutic agents should be *considered*, and if indicated, administered: (a) hypertonic dextrose 0.5–1.0 g/kg of $D_{50}W$ for an adult, or a more dilute dextrose solution ($D_{10}W$ or $D_{25}W$) for a child. The dextrose is administered to diagnose and treat or exclude hypoglycemia; (b) thiamine 100 mg IV for an adult (usually unnecessary for a child) to prevent or treat Wernicke encephalopathy; (c) titrated naloxone beginning at 0.05 mg IV for an adult or child with suspected opioid-induced respiratory compromise; and (d) high-flow oxygen (8–10 L/min) to treat hypoxia.

The physical examination should be performed rapidly, but thoroughly. Key elements of the directed examination include an evaluation of the pupil size and reactivity, skin moisture, bowel sounds, bladder size (urinary retention), and mental status. Characteristic breath or skin odors may identify the etiology of coma, such as the minty odor of oil of wintergreen on the breath or skin suggesting methyl salicylate poisoning. The Glasgow Coma Scale (GCS) should never be used for prognostic purposes, because complete recovery from properly managed toxic-metabolic coma despite a low GCS is the rule rather than the exception.

Repeated reevaluation of the patient suspected of an overdose is essential for identifying new or developing findings or toxic syndromes, and for early identification and treatment of a deteriorating condition. Until the patient is completely recovered or considered no longer at risk for the consequences of a toxic exposure, frequent reassessment must be provided, even as the procedures described below are carried out. At this point a decision about the need for, and method of gastrointestinal decontamination or enhanced elimination can be made based upon pertinent components of the history, physical examination, and screening tests mentioned above. A consideration of available antidotes should follow.

AVOIDING PITFALLS IN MANAGING A PATIENT WITH A SUSPECTED TOXIC EXPOSURE

The history alone is not a reliable indication of which patients require naloxone, hypertonic dextrose ($D_{50}W$), thiamine, and oxygen. Instead, these therapies should be *considered* for all patients with altered mental status, unless specifically contraindicated. The physical examination should be used to guide the use of naloxone. Although CNS depression, miosis, and respiratory depression are characteristic, existing data suggests that respiratory depression (defined as a respiratory rate of ≤12 breaths/min) is the best predictor of response. If dextrose or naloxone is indicated, sufficient amounts should be administered to exclude and/or treat hypoglycemia or opioid toxicity, respectively.

In a patient with a suspected or unknown overdose, avoid the use of vasopressors in the initial management of hypotension prior to administering fluids or assessing filling pressures.

Attributing an altered mental status to ethanol because of its odor on a patient's breath is potentially dangerous and misleading because small amounts of ethanol and its congeners generally produce the same breath odor as do intoxicating amounts. Conversely, even when an extremely high blood-ethanol concentration is *confirmed* by the laboratory, it is dangerous to ignore other possible etiologies of an altered mental status; chronic alcoholics may be awake and seemingly alert with ethanol levels in excess of 500 mg/dL, a level that would result in coma and possibly apnea and death in an ethanol-naive patient.

The metabolism of ethanol is fairly constant at 15–30 mg/dL/h. Therefore, as a general rule, regardless of the initial blood ethanol concentration, a presumably "inebriated" comatose patient who is still unarousable 3–4 hours after arrival should be considered to have structural CNS damage (head trauma) and/or another toxic-metabolic etiology for the alteration in consciousness, until proven otherwise. Careful neurologic reevaluation supplemented by a head CT scan is frequently indicated in such a case. This is especially important in dealing with a seemingly "intoxicated" patient who appears to have only a minor bruise, as the early treatment of a subdural or epidural hematoma or subarachnoid hemorrhage is critical to a successful outcome.

SPECIAL CONSIDERATIONS FOR MANAGING THE PREGNANT PATIENT WITH A TOXIC EXPOSURE

In general, a successful outcome for both mother and fetus is dependent on optimum management of the mother. Proven effective treatment for a potentially serious toxic exposure in the mother should never be withheld based on theoretical concerns regarding the fetus.

Use of Antidotes

Few data are available on the use of antidotes in pregnancy. In general, antidotes should not be used if the indications for use are equivocal. On the other hand, antidotes should not be withheld if their use may reduce potential morbidity and mortality for the mother.

MANAGEMENT OF PATIENTS WITH A TOXIC CUTANEOUS EXPOSURE

The xenobiotics that people are commonly exposed to externally include household cleaning materials; organic phosphorus or carbamate insecticides from crop dusting, gardening, and pest extermination; acids from leaking or

exploding batteries; alkalis such as lye; and lacrimating agents that are used in crowd control. In all cases, the principles of management are as follows:

1. The staff should avoid secondary exposures by wearing protective (rubber or plastic) gowns, gloves, and shoe covers. Cases of serious secondary poisoning have occurred in emergency personnel after contact with xenobiotics such as organic phosphorus compounds on the victim's skin or clothing.
2. The patient's clothing should be removed and placed in plastic bags, which are then sealed.
3. The patient should be washed with soap and copious amounts of water twice, regardless of how much time has elapsed since the exposure.
4. No attempt should be made to neutralize an acid with a base, or a base with an acid. Further tissue damage may result from the heat generated by this reaction.
5. The use of all highly viscous materials or creams should be avoided, as they will only keep the xenobiotic in close contact with the skin, ultimately making removal more difficult.

MANAGEMENT OF PATIENTS WITH TOXIC OPHTHALMIC EXPOSURES

Although the vast majority of toxicologic emergencies result from ingestion, injection, or inhalation, the eyes and skin are occasionally the routes of systemic absorption or are the organs at risk. The eyes should be irrigated with lids fully retracted for no less than 10–20 minutes. To facilitate irrigation, a local anesthetic should be used.

IDENTIFYING THE PATIENT WITH A NONTOXIC EXPOSURE

More than 40% of exposures reported to poison centers are judged to be nontoxic. The following general guidelines for considering an exposure nontoxic or minimally toxic will assist clinical decision making:

1. Identification of the product and its ingredients is possible.
2. The Consumer Product Safety Commission (CPSC) "signal words" CAUTION, WARNING, or DANGER does not appear on the product label.
3. The history permits the route(s) of exposure to be determined.
4. The history permits a reliable approximation of the maximum quantity involved with the exposure.
5. Based on the available medical literature and clinical experience, the potential effects related to the exposure are expected to be at most benign and self-limited, and do not require referral to a healthcare facility.
6. The patient is asymptomatic, or has developed the expected benign self-limited toxicity.

5 Electrocardiographic Principles

The electrocardiogram (ECG) is ubiquitous in emergency departments and intensive care units, and its interpretation is widely understood by physicians of nearly all disciplines. It is a valuable source of information in poisoned patients and has the potential to enhance and direct their care. Although it seems obvious that an ECG is required following exposure to a drug used for cardiovascular indications, many drugs with no overt cardiovascular effects from therapeutic dosing become cardiotoxic in overdose. An ECG should be examined critically early in the initial evaluation of most poisoned patients.

BASIC ELECTROPHYSIOLOGY OF THE MYOCARDIAL CELL

Figure 5–1 shows schematically the relationship of the major ion fluxes across the myocardial cell membrane, the phases of the action potential, and the surface ECG recording. Chap. 23 provides a more detailed description of ion fluxes and channels.

BASIC ELECTROPHYSIOLOGY OF AN ELECTROCARDIOGRAM

An electrocardiogram represents the sum of movement of all electrical forces in the heart in relation to the surface electrode and the height above baseline represents the magnitude of the force (Fig. 5–2). Only during depolarization or repolarization does the electrocardiogram tracing leave the isoelectric baseline, because it is only during these periods that measurable currents are flowing in the heart. During the other periods, mechanical effects are occurring in the myocardium, but large amounts of current are not flowing.

The Various Intervals and Waves

The ECG tracing has specific nomenclature to define the characteristic patterns. Waves refer to positive or negative deflections from baseline, such as the P, T, or U wave. A segment is defined as the distance between two waves, such as the ST segment, and an interval measures the duration of a wave plus a segment, such as QT or PR interval. Complexes are a group of waves without intervals or segments between them (QRS). Electrophysiologically, the P wave and PR interval on the ECG tracing represent the depolarization of the atria. The QRS complex represents the depolarization of the ventricles. The plateau is depicted by the ST segment, and repolarization is visualized as the T wave and the QT interval (QTc). The U wave, when present, generally represents an afterdepolarization (Fig. 5–3).

The Abnormal P Wave

Clinically, abnormalities of the P wave occur with agents that depress automaticity of the sinus node, causing sinus arrest and nodal or ventricular escape rhythms (β-adrenergic antagonists, calcium channel blockers). The P wave is absent in rhythms with sinus arrest, such as occurs with xenobiotics that produce vagotonia such as cardioactive steroids and cholinergics. A notched P wave suggests delayed conduction across the atrial septum and is characteristic of quinidine poisoning. P waves decrease in amplitude as hy-

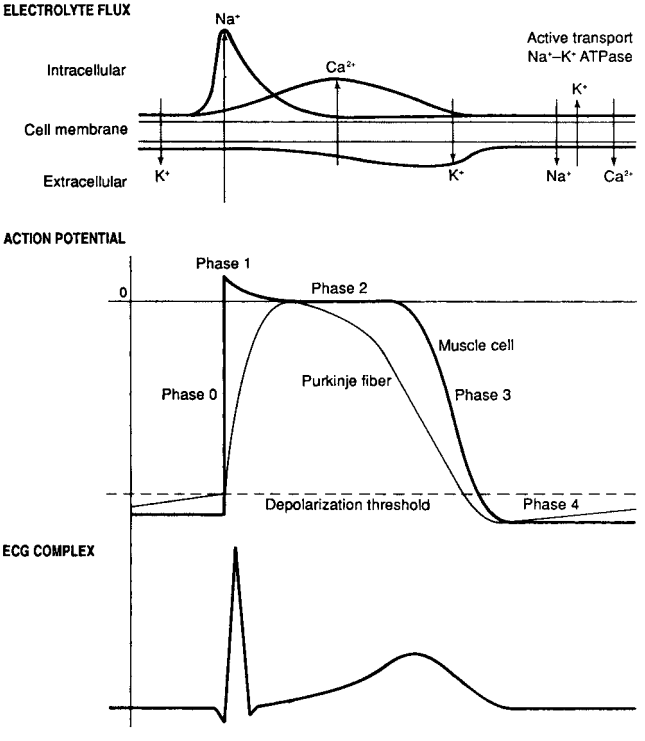


FIG. 5–1. Relationship of electrolyte movement across the cell membrane to the action potential and the surface ECG recording.

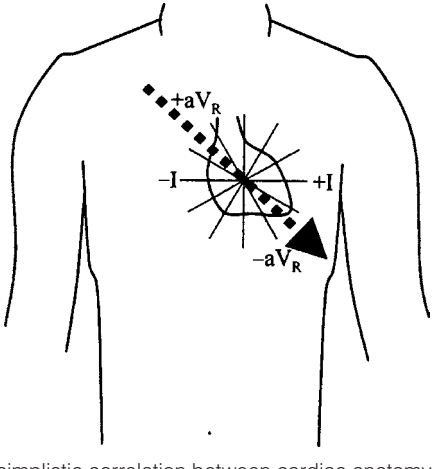


FIG. 5–2. A simplistic correlation between cardiac anatomy and electrocardiographic representation.

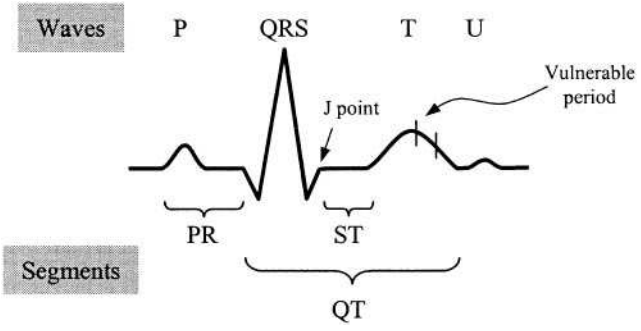


FIG. 5–3. The normal ECG: P wave, atrial depolarization; QRS, ventricular depolarization; ST segment, T wave, QT interval, and U wave, ventricular repolarization. The U wave is the small, positive deflection following the T wave.

perkalemia becomes more severe until they become indistinguishable from the baseline (Chap. 17).

The Abnormal PR Interval

Agents that decrease interatrial or atrioventricular (AV) nodal conduction cause marked lengthening of the PR segment until such conduction completely ceases. At this point, the P wave no longer relates to the QRS complex; this is AV dissociation or complete heart block. Some xenobiotics suppress AV nodal conduction by blocking calcium channels in nodal cells, as do magnesium and calcium channel blockers, antagonizing β-adrenergic receptors, or enhancing vagal tone. Although the therapeutic use of digoxin, as well as early cardioactive steroid poisoning, causes PR prolongation through vagotonic effects, direct electrophysiologic effects account for the bradycardia of poisoning (see later in this chapter, as well as Chap. 62 and Antidotes in Brief: Digoxin-Specific Antibody Fragments [Fab]).

The Abnormal QRS Complex

In the presence of a bundle-branch block, the two ventricles depolarize sequentially rather than concurrently. Although conceptually conduction through either the left or right bundle may be affected, many xenobiotics preferentially affect the right bundle. This effect typically results in the left ventricle depolarizing slightly more rapidly than the right ventricle. The consequence on the ECG is both a widening of the QRS complex and the appearance of the right ventricular electrical forces that were previously obscured by those of the left ventricle. These changes are often a result of the effects of xenobiotics that block fast sodium channels. Implicated xenobiotics include cyclic antidepressants, quinidine and other type IA and IC antidysrhythmics, phenothiazines, amantadine, diphenhydramine, carbamazepine, and cocaine. In the setting of tricyclic antidepressant (TCA) poisoning, this finding has both prognostic and therapeutic value (Chap. 71). Specifically, in a prospective analysis of ECGs the maximal limb lead QRS duration was prognostic of seizures (0% if <100 msec; 30% if >100 msec) and ventricular dysrhythmias (0% if <160 msec; 50% if >160 msec).

This terminal 40-msec axis of the QRS complex contains critical information regarding the likelihood, not the extent, of poisoning by sodium channel blockers.

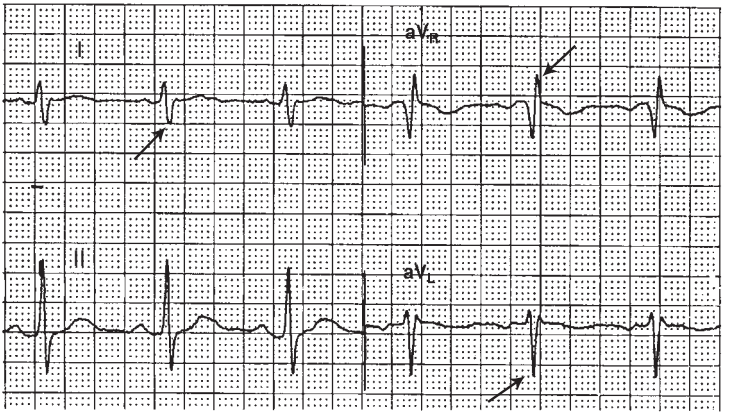


FIG. 5–4. ECG showing leads I, II, aV_R, and aV_L of a patient with a TCA overdose. The prominent S wave in leads I and aV_L, and R wave in aV_R, demonstrate the terminal 40-msec rightward axis shift.

In a poisoned patient, the common abnormalities include an R wave (positive deflection) in lead aV_R and an S wave (negative deflection) in leads I and aV_L. The terminal portion of the QRS has a rightward deviation greater than 120°. The combination of a rightward axis shift in the terminal 40 msec of the QRS complex (Fig. 5–4) along with a prolonged QTc and a sinus tachycardia is highly specific and sensitive for TCA poisoning. Absence of these findings, in one study at least, excluded serious TCA poisoning. Another study suggests that although ECG changes, like a prolonged QRS duration, are better at predicting severe outcomes than the TCA level, neither is very accurate. One prospective study suggests that an absolute height of the terminal portion of aV_R that is >3 mm, predicted seizures or dysrhythmias in TCA-poisoned patients. In infants younger than 6 months of age, however, a rightward deviation of the terminal 40-msec QRS axis is physiologic and not predictive of TCA toxicity. In older children, a retrospective chart review of 37 children diagnosed with TCA overdose and 35 controls (all younger than 11 years old) found such interpatient variability, unrelated to age, so great that a rightward deviation of the terminal 40-msec QRS axis could not distinguish between poisoned and healthy children.

An apparent increase in QRS duration and morphology, which is actually an elevation or distortion of the J point called a J wave or an Osborn wave (Fig. 16–1), is a common finding in patients with hypothermia. Hypermagnesemia is also associated with a widening of the QRS duration, and a slight narrowing of the QRS complex may occur with hypomagnesemia. Significant elevation in the serum concentrations of potassium can also cause widening and distortion of the QRS complex.

The Abnormal ST Segment

Displacement of the ST segment from its baseline characterizes myocardial ischemia or infarction (Fig. 5–5). The subsequent appearance of a Q wave is diagnostic of myocardial infarction. The ECG patterns of these entities reflect the different underlying electrophysiologic states of the heart. Ischemic re-

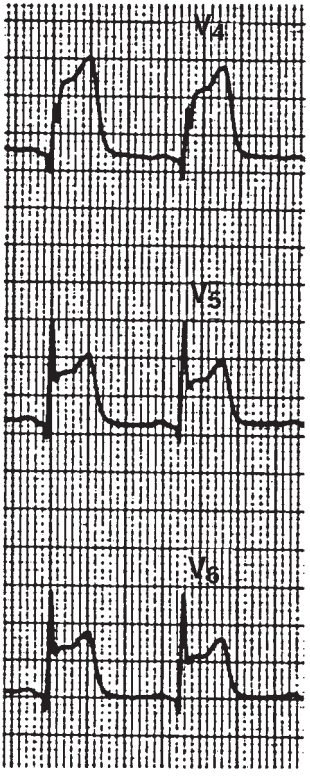


FIG. 5–5. Leads V_4–V_6 are shown from the ECG of a 27-year-old man with substernal chest pain after using crack cocaine.

gions are highly unstable and produce currents of injury because of inadequate repolarization, which is related to lack of energy substrate to power the Na^+-K^+ adenosine triphosphatase (ATPase). Infarction represents the loss of electrical activity from the necrotic, inactive ventricular tissue, allowing the contralateral ventricular forces to be predominant on the ECG. Patients who are poisoned by xenobiotics that cause vasoconstriction, such as cocaine (Chap. 74), other α-adrenergic agonists, or the ergot alkaloids, are particularly prone to develop focal myocardial ischemia and infarction. The specific electrocardiographic manifestations help to identify the region of injury and may, to some extent, be correlated with an arterial flow pattern: inferior (leads II, III, aV_F; right coronary artery), anterior (leads I, aV_L; left anterior descending artery), or lateral (leads aV_L, $V_{5–6}$; circumflex branch). However, any poisoning that results in profound hypotension or hypoxia can also result in ECG changes of ischemia and injury. In this situation, the injury may be more global, involving more than one arterial distribution. Diffuse myocardial damage may not be identifiable on the electrocardiogram because there are global, symmetric electrical abnormalities. In this situation, the diagnosis

is made by other noninvasive testing, such as by echocardiogram or by finding elevations in serum markers for myocardial injury (eg, troponin).

Many young, healthy patients have ST segment abnormalities that mimic those of myocardial infarction. The most common normal variant is termed "early repolarization" or "J-point elevation," and is identified as diffusely elevated, upwardly concave ST segments, located in the precordial leads and typically with corresponding T waves of large amplitude. The J point is located at the beginning of the ST segment just after the QRS complex. Because this electrocardiographic variant is common in patients with cocaine-associated chest pain (Chap. 67), its recognition is critical to instituting appropriate therapy.

Blockade of the fast sodium channel is characterized by terminal positivity of the QRS complex and ST-segment elevation in the right precordial leads (Fig. 5–6). This ECG pattern often occurs in patients who are poisoned by sodium channel blockers, including TCAs, cocaine, and class IA (procainamide) and class IC (flecainide, encainide) antidysrhythmics. In TCA-poisoned patients this pattern is associated with an increased risk of hypotension, but not sudden death or dysrhythmias. Sagging ST segments, inverted T waves, and normal or shortened QT intervals are characteristic effects of cardioactive steroids, such as digoxin, on the electrocardiogram. These repolarization abnormalities are sometimes identified by their similar appearance to "Salvador Dali's mustache." As a group, these findings, along with PR prolongation, are commonly described as the "digitalis effect" (Chap. 62). They are found in patients with therapeutic drug concentrations and in patients with cardioactive steroid poisoning. As the serum, or more precisely the tissue concentration increases, clinical and electrocardiographic manifestations of toxicity appear (Chap. 62), the latter of which includes profound bradycardia or ventricular dysrhythmias.

Changes in the ST-segment duration are frequently caused by abnormalities in the serum calcium concentration. Hypercalcemia causes shortening of the ST segment through enhanced calcium influx during the plateau phase of the cardiac cycle speeding the onset of repolarization. For practical purposes this effect is more commonly identified by reduction of the corrected QT[QTc]. In patients with hypercalcemia, the morphology and durations of the QRS complex and T and P waves remain essentially unchanged. Drug-induced hypercalcemia may result from exposure to antacids (milk alkali syndrome), diuretics (eg, hydrochlorothiazide), cholecalciferol (vitamin D), vitamin A, and other retinoids. Hypocalcemia causes prolongation of the ST segment and QTc interval.

The Abnormal T Wave

Isolated peaked T waves are usually evidence of early hyperkalemia. Hyperkalemia initially causes tall, tented T waves with normal QRS, QTc, and P wave. As the measured potassium rises to 6.5–8 mEq/L, the P wave diminishes in amplitude and the PR and QRS intervals prolong. Progressive widening of the QRS complex causes it to merge with the ST segment and T wave, forming a "sine wave." Electrocardiographic manifestations of hyperkalemia may occur following chronic exposure to numerous medications, including potassium-sparing diuretics, angiotensin-converting enzyme inhibitors (Chap. 60), or potassium supplements. Either fluoride or cardioactive steroid poisoning produces acute hyperkalemia, but the latter rarely produces hyperkalemic electrocardiogram changes (Chap. 17). Peaked T waves also occur following myocardial ischemia and may also be confused with early repolarization effects. Thus, the ability to properly identify electrolyte abnormalities by electrocardiography is often limited.

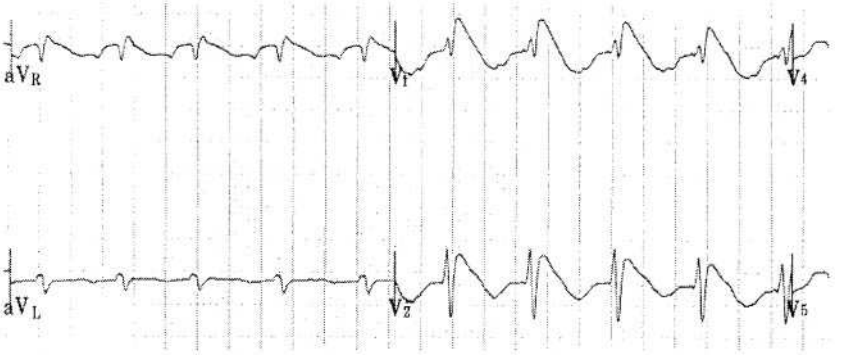


FIG. 5–6. The Brugada pattern is characterized by terminal positivity of the QRS complex and ST-segment elevation in the right precordial leads, and is an ECG pattern similar to that noted in patients poisoned by sodium channel blocking agents such as TCAs. (Reproduced with permission of Vikhyat Bebarta, MD.)

Hypokalemia typically reduces the amplitude of the T wave and, ultimately, causes the appearance of prominent U waves. Its effects on the electrocardiogram are manifestations of altered myocardial repolarization. Lithium similarly affects myocardial ion fluxes and causes reversible changes on the electrocardiogram that may mimic mild hypokalemia, although documentation of low cellular potassium concentrations is lacking. Patients chronically poisoned with lithium have more T-wave abnormalities (typically flattening) than do those who are acutely poisoned, but these are rarely of clinical significance.

The Abnormal QT Interval

A prolonged QT interval reflects an increase in the time period that the heart is "vulnerable" to the initiation of ventricular dysrhythmias (Fig. 5–6). This occurs because although some myocardial fibers are refractory during this time period, others are not (ie, relative refractory period). Early afterdepolarizations may occur in patients with lengthened repolarization time (Table 5–1). An "early afterdepolarization" (EAD) occurs when a myocardial cell spontaneously depolarizes before its repolarization is complete (Fig. 5–7). If this depolarization is of sufficient magnitude it may capture and initiate a premature ventricular contraction, which itself may initiate ventricular tachycardia, ventricular fibrillation, or torsades de pointes. There are two types of EADs that occur either when the membrane potential is decreased during phase 2 (type 1) and phase 3 (type 2) of the cardiac action potential. The ionic basis of EADs is unclear, but may be via the L-type calcium channel; EADs are suppressed by magnesium.

Xenobiotics that cause sodium channel blockade (Chap. 61), prolong the QT duration by slowing cellular depolarization during phase 0. Thus, the QT duration increases as a result of a prolongation of the QRS complex duration, and the ST-segment duration remains near normal. Xenobiotics that cause potassium channel blockade similarly prolong the QT interval, but through prolongation of the plateau and repolarization phases. This specifically prolongs

TABLE 5–1. The Electrophysiologic Basis for Delayed Afterdepolarization and Early Afterdepolarization

	Phase of Action Potential Affected by Depolarization	Clinical Effect	Mechanism
Delayed after depolarization (DAD)	Phase 4	Cardioactive steroid–induced dysrhythmias	Intracellular Ca^{2+} → activation of a nonselective cation channel or Na^{+} -Ca^{2+} exchanger → transient inward current carried mostly by Na^{+} ions
Early after depolarization (EAD)		↑ Repolarization time. Long QT syndrome (hereditary and acquired)	Possibly via L-type calcium channels
Type 1 Type 2	Phase 2 Phase 3	Drug-induced torsades de pointes, ventricular tachycardia	Suppressed by magnesium

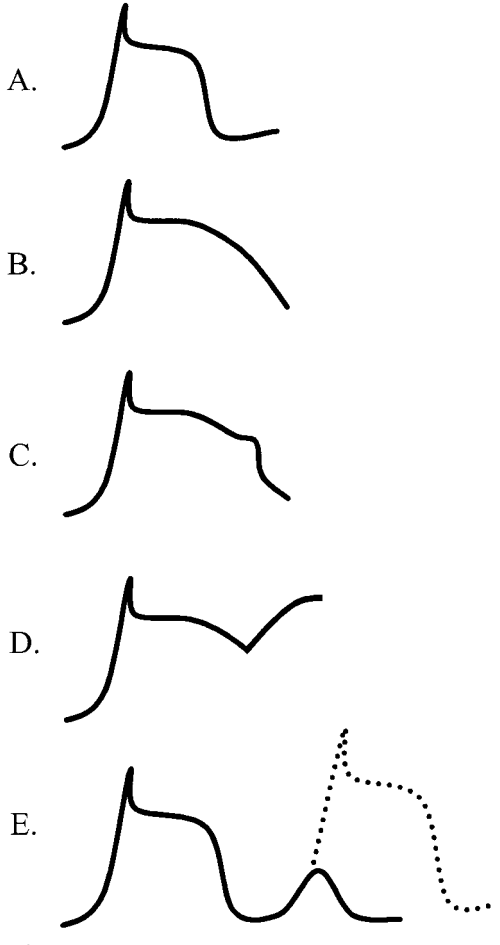


FIG. 5–7. Afterdepolarization. **A.** The normal action potential. **B.** Prolonged duration action potential. **C.** Prolonged duration action potential with an early afterdepolarization (EAD) occurring during the downslope of phase 3 of the action potential. **D.** EAD that reaches the depolarization threshold and initiates another depolarization, or a triggered beat. **E.** Delayed afterdepolarization, which occurs after repolarization is complete.

the ST-segment duration. Although at a cellular level these xenobiotics are antidysrhythmic, the multicellular effects may be prodysrhythmic.

Hypocalcemia is caused by a number of xenobiotics, including fluoride, calcitonin, ethylene glycol, phosphates, and mithramycin (Table 17–9). Hypokalemia and hypomagnesemia alone do not usually prolong the QT interval. Arsenic poisoning may cause prolongation of the QT interval and torsades de pointes. The mechanism is unknown, although either a direct dysrhythmogenic effect or an autoimmune myocarditis is postulated.

The Abnormal U Wave

Abnormal U waves are typically caused by spontaneous afterdepolarization of membrane potential that occurs in situations where repolarization is prolonged. EAD occurs in situations where the prolonged repolarization period allows calcium channels (which are both time and voltage dependent) to close and spontaneously reopen, because they may close at a membrane potential that is above their threshold potential for opening. In this situation, the opening of the calcium channels produces a slight membrane depolarization that is identified as a U wave. Delayed afterdepolarization occurs when the myocyte is overloaded with calcium, as in the setting of cardioactive steroid toxicity. The excess intracellular calcium can trigger the ryanodine receptors on the myocyte sarcoplasmic reticulum to release calcium, causing slight depolarization that is recognized as a U wave. If the U waves are of sufficient magnitude to reach threshold, the cell may depolarize and initiate a premature ventricular contraction. Transient U-wave inversion can also be caused by myocardial ischemia or hypertension.

The Abnormal QU Interval

The QU interval is the distance between the end of the Q wave and the end of the U wave. Differentiation between the QU and the QT intervals is difficult if the T and U waves are superimposed. When hypomagnesemia coexists with hypokalemia, as is usually the case, QU prolongation and torsades de pointes may occur.

ELECTROCARDIOGRAM DISTURBANCES

The distinction between xenobiotics that cause a rapid rate and those that cause a slow rate on the ECG is somewhat artificial, because many can do both. For example, patients poisoned by TCAs almost always develop sinus tachycardia, but most die with a wide complex bradycardia. Regardless, abnormalities in the pattern or rate on the electrocardiogram can provide the clinician with immediate information about a patient's cardiovascular status. Any rhythm other than normal sinus rhythm is referred to as a dysrhythmia in this text. Electrocardiographic disturbances in many poisoned patients may be categorized in more than one manner (abnormal pattern, fast rate, slow rate). Regardless, when electrocardiographic abnormalities are detected, appropriate interpretation, evaluation, and therapy must be rapidly performed.

Tachydysrhythmias

The intrinsic pacemaker cells of the heart undergo spontaneous depolarization and reach threshold at a predictable rate. Under normal circumstances, the sinus node is the most rapidly firing pacemaker cell of the heart; because of this, it controls the heart rate. Spontaneous depolarization occurs during ion entry through potassium, sodium, and calcium channels during phase 4 of the action potential. Other potential pacemakers exist in the heart, but their rate of spontaneous depolarization is considerably slower than that of the sinus node. Consequently, they are reset during depolarization of the myocardium and they never spontaneously reach threshold. Xenobiotics that speed the rate of rise of phase 4, or diastolic depolarization, speed the rate of firing of the pacemaker cells. As long as the sinus node is preferentially affected, it maintains the pacemaker activity of the heart. If the firing rate of another intrinsic pacemaker exceeds that of the sinus node, ectopic rhythms may de-

velop. This effect may be either pathologic or lifesaving, depending on the clinical circumstances.

The rate of impulse formation at the sinus node is regulated by the balance between parasympathetic and sympathetic tone. The influences of these parts on the autonomic nervous system are responsible for regulating the heart rate under normal conditions. Sympathomimetics, such as norepinephrine, cocaine, and amphetamines, increase sympathetic tone, producing sinus tachycardia and enhancing AV nodal conduction. Sinus tachycardia may be the first manifestation of exposure to a sympathomimetic. However, other supraventricular or ventricular dysrhythmias may develop if an abnormal rhythm is generated in another part of the heart. Similarly, xenobiotics that antagonize acetylcholine released from the vagus nerve onto the sinus node enhance the rate of firing, producing sinus tachycardia. Such xenobiotics include the belladonna alkaloids atropine and scopolamine, first-generation antihistamines, and the TCAs. Table 23–4 lists a wide variety of xenobiotics that often cause tachydysrhythmias.

Certain xenobiotics are more highly associated with ventricular tachydysrhythmias following poisoning. Those that alter myocardial repolarization and prolong the QTc predispose to the development of afterdepolarization-induced contractions during the relative refractory period (R-on-T phenomena), which initiates ventricular tachycardia. If torsades de pointes is noted, this is undoubtedly the mechanism, and the QTc should be carefully assessed and appropriate treatment initiated. Alternatively, xenobiotics that increase the adrenergic tone on the heart, either directly or indirectly, may cause ventricular dysrhythmias. Whether a result of excessive circulating catecholamines observed with cocaine and sympathomimetics, myocardial sensitization secondary to halogenated hydrocarbons or thyroid hormone, or increased second-messenger activity secondary to theophylline, the extreme inotropic and chronotropic effects cause dysrhythmias. Altered repolarization, increased intracellular calcium concentrations, or myocardial ischemia may cause the dysrhythmia. Additionally, xenobiotics that produce focal myocardial ischemia, such as cocaine or ephedrine, can lead to malignant ventricular dysrhythmias. Finally, an uncommon cause of xenobiotic-induced ventricular dysrhythmias is persistent activation of sodium channels, with the distinguishing electrocardiographic findings that occur following aconitine poisoning. Not all wide QRS complex tachydysrhythmias are ventricular in origin, but making this assumption is generally considered to be prudent. For example, in a patient known to be poisoned with TCAs, cocaine, or similar xenobiotics, the differentiation of aberrantly conducted sinus tachycardia (common) from ventricular tachycardia (rare) is important, but difficult. Although guidelines for determining the origin of a wide complex tachydysrhythmia exist, they are imperfect, difficult to apply, and unstudied in poisoned patients.

Bidirectional ventricular tachycardia is associated with severe cardioactive steroid toxicity and results from alterations of intraventricular conduction, junctional tachycardia with aberrant intraventricular conduction, or, on rare occasions, alternating ventricular pacemakers. The only other xenobiotic that commonly causes this dysrhythmia is aconitine, usually obtained from traditional or alternative therapies that contain the plant Aconitum (Chaps. 43 and 114).

Bradydysrhythmias

Bradycardia and asystole are the terminal events following fatal ingestions of many xenobiotics, although some tend to cause sinus bradycardia (Table 23–1) and conduction abnormalities (Table 23–2) early in the course of toxicity. Si-

nus bradycardia with an otherwise normal electrocardiogram is characteristic of xenobiotics that reduce central nervous system outflow. Examples include benzodiazepines, ethanol, and clonidine, and differentiating between these agents is not possible based on electrocardiographic criteria alone. Xenobiotics that directly affect ion flux across myocardial cell membranes cause abnormalities in AV nodal conduction. Calcium channel blockers, β-adrenergic antagonists, and cardioactive steroids (Chaps. 58–60) are the leading causes of sinus bradycardia and conduction disturbances.

The ECG manifestations of calcium channel blocker and β-adrenergic antagonist overdoses are difficult to distinguish. In general, both drug classes cause decreased dromotropy (conduction), although the specific pharmacologic actions of the drugs differ even within the class (Chaps. 58 and 59). For example, most members of the dihydropyridine subclass of calcium channel blockers do not have any antidromotropic effect, whereas verapamil and diltiazem routinely produce PR prolongation. Similarly, although most β-adrenergic antagonists produce sinus bradycardia and first-degree heart block, certain members of this group, such as propranolol, may prolong the QRS complex through their sodium channel blocking abilities. Others, such as sotalol, which have properties of the class III (Chap. 61) agents, block myocardial potassium channels and prolong the QT interval duration. The bradycardia produced by cardioactive steroids is typically accompanied by signs of "digitalis effect" including PR prolongation and ST segment depression (Chap. 62).

Ectopy

Ectopy is the electrocardiographic manifestation of myocardial depolarization initiated from a site other than the sinus node. Ectopy may be lifesaving under circumstances in which the atrial rhythm cannot be conducted to the ventricles, as during high-degree AV blockade induced by cardioactive steroids. Alternatively, ectopy may lead to dramatic alterations in the physiologic function of the heart or deteriorate into lethal ventricular dysrhythmias.

Several mechanisms by which ectopic rhythms may develop are noted. An impulse that occurs after completion of repolarization (phase 4) is called a "delayed afterdepolarization" (DAD) (Fig. 5–7 and Table 5–1). The mechanism of DADs is related to increases in intracellular calcium that activate a nonselective cation channel or an electrogenic Na^+-Ca^{2+} exchanger that causes a transient inward current carried primarily by sodium ions. This inward sodium current generates the DAD. The increased calcium concentrations may come from extensive sympathetic stimulation, large doses of a cardioactive steroid, or other abnormal physiologic conditions. Delayed afterdepolarizations are the likely cause of some dysrhythmias induced by cardioactive steroid poisoning (Chap. 62). Compared with EADs, DADs generally arise when the membrane potential is more negative.

6 Diagnostic Imaging

Diagnostic imaging can play a significant role in the management of many toxicologic emergencies. In some cases, radiographic studies can directly visualize the xenobiotic, whereas in others, they reveal the xenobiotic's effect on various organ systems. Radiography can confirm a diagnosis, assist in therapeutic interventions such as monitoring gastrointestinal decontamination, and detect complications of the xenobiotic exposure.

VISUALIZING THE XENOBIOTIC

A number of xenobiotics are *radiopaque* and can potentially be detected by conventional radiography. If ingested, the xenobiotic may be seen on an abdominal radiograph. Radiopaque xenobiotics that have been injected are also amenable to radiographic detection. If the toxic material is available for examination, it can be radiographed outside of the body to detect any radiopaque contents.

The radiopacity of a xenobiotic is determined by several factors. First, the *intrinsic radiopacity* of a substance depends on its physical density (g/cm^3) and the atomic numbers of its constituent atoms. Biologic tissues are composed mostly of carbon, hydrogen, and oxygen, and have an average atomic number of approximately 6. Substances that are more radiopaque than soft tissues include bone, which contains calcium (atomic number 20); radiocontrast agents containing iodine (atomic number 53) and barium (atomic number 56); iron (atomic number 26); and lead (atomic number 82). Some medications and xenobiotics have constituent atoms of high atomic number, such as chlorine (atomic number 17), potassium (atomic number 19), and sulfur (atomic number 16), which contribute to their radiopacity.

The thickness of an object affects its radiopacity. Small particles of a moderately radiopaque substance are often not visible on a radiograph. The radiographic appearance of the surrounding area also affects the detectability of an object. A moderately radiopaque tablet is easily seen against a uniform background, but in a patient, overlying bone or bowel gas often obscures the tablet.

Although a clinical policy issued by the American College of Emergency Physicians in 1995 suggested that an abdominal radiograph should be obtained in the unresponsive overdosed patient in an attempt to identify the involved xenobiotic, the role of abdominal radiography in screening patients who have ingested an unknown substance is questionable. The number of potentially ingested substances that are radiopaque is limited. However, when ingestion of a radiopaque substance such as iron tablets or heavy metals is suspected, abdominal radiographs are helpful. A short list of the more consistently radiopaque substances is summarized in the mnemonic CHIPES: chloral hydrate, heavy metals, iron, psychotropics (phenothiazines), and enteric-coated and sustained-release preparations. In contrast, a radiolucent substance may be visible because it is less radiopaque than surrounding soft tissues. Hydrocarbons such as gasoline are relatively radiolucent when embedded in soft tissues. The radiographic appearance resembles subcutaneous gas as seen in a necrotizing soft-tissue infection.

VISUALIZING THE EFFECTS OF A XENOBIOTIC ON THE BODY

Skeletal Changes Caused by Xenobiotics

A number of xenobiotics affect bone mineralization. Toxicologic effects on bone result in either increased or decreased density. Some xenobiotics produce a characteristic radiographic picture, although the exact diagnosis usually depends on correlation with the clinical scenario. Furthermore, alterations in skeletal structure develop gradually and are usually not visible unless the exposure continues for at least two weeks. Clinically important examples include lead, fluoride, alcoholism, corticosteroids, vinyl chloride monomer, and infectious diseases associated with injection drug use.

Pulmonary and Other Thoracic Complications

Many xenobiotics that affect intrathoracic organs produce pathologic changes that can be detected on chest radiographs. The lungs are most often affected, but the pleura, hilum, heart, and great vessels may also be involved. Patients with chest pain may have a pneumothorax, pneumomediastinum, or aortic dissection. Patients with fever with or without respiratory symptoms may have a focal infiltrate, pleural effusion, or hilar lymphadenopathy.

The chest radiographic findings will suggest certain diseases, although the diagnosis ultimately depends on a thorough clinical history.

Many pulmonary disorders are radiographically detectable because they result in fluid accumulation within the alveolar spaces or interstitial tissues of the lung, producing the two major radiographic patterns of pulmonary disease—airspace filling and interstitial lung disease.

Diffuse Airspace Filling

Overdose with salicylates, opioids, and paraquat, causes *acute lung injury*, which, pathologically, is characterized by leaky capillaries. There are many other causes of acute lung injury, including sepsis, anaphylaxis, and major trauma. Other xenobiotic exposures that result in diffuse airspace filling include inhalation of irritant gases that are of low water solubility such as phosgene ($COCl_2$), nitrogen dioxide (silo filler disease), chlorine, and sulfur dioxide. Organic phosphorus insecticide poisoning causes cholinergic stimulation, resulting in bronchorrhea. Smoking "crack" cocaine is associated with diffuse intrapulmonary hemorrhage.

Focal Airspace Filling

Most focal infiltrates are caused by bacterial pneumonia, although aspiration of gastric contents also causes localized airspace disease. Low-viscosity hydrocarbons often enter the lungs when they are swallowed. Because of the delay in development of radiographic abnormalities, the chest radiograph may not be abnormal until six hours after the ingestion.

Interstitial Lung Diseases

Toxicologic causes of interstitial lung disease include hypersensitivity pneumonitis, medications with direct pulmonary toxicity, and inhalation or injection of inorganic particulates. In hypersensitivity pneumonitis the chest radiograph is normal or may show fine interstitial or alveolar infiltrates. The most common medication causing hypersensitivity pneumonitis is nitrofurantoin. Sulfonamides and penicillins are other medications that can cause hypersen-

sitivity pneumonitis. Various chemotherapeutic agents, such as busulfan, bleomycin, cyclophosphamide, and methotrexate, cause pulmonary injury by their direct cytotoxic effect on alveolar cells. The radiographic pattern is usually interstitial (reticular or nodular), but can include airspace filling or mixed patterns. Amiodarone toxicity causes phospholipid accumulation within alveolar cells and can cause pulmonary fibrosis. An interstitial radiographic pattern is seen, although airspace filling can also occur.

Pleural Disorders

Asbestos-related calcified pleural plaques develop many years after asbestos exposure. Asbestos-related pleural plaques should not be called "asbestosis" because that term refers specifically to the interstitial lung disease caused by asbestos. Pleural plaques must be distinguished from a mesothelioma, which is not calcified, enlarges at a rapid rate, and erodes into nearby structures such as the ribs. *Pleural effusions* may occur in drug-induced systemic lupus erythematosus. The medications most frequently implicated are procainamide, hydralazine, isoniazid, methyldopa, and chlorpropamide. *Pneumothorax* and *pneumomediastinum* are associated with illicit drug use, and are related to the route of administration rather than to the particular drug. Barotrauma results from either a Valsalva maneuver or intense inhalation with breath holding during the smoking or inhalation.

Cardiovascular Abnormalities

Dilated cardiomyopathy occurs in chronic alcoholism and exposure to cardiotoxic medications such as doxorubicin. Enlargement of the cardiac silhouette can also be caused by a pericardial effusion, which can accompany a drug-induced systemic lupus erythematosus. *Aortic dissection* is associated with use of cocaine. The chest radiograph may show an enlarged or indistinct aortic knob or ascending or descending aorta.

Abdominal Complications

Abdominal imaging modalities include conventional radiography, CT, GI contrast studies, and angiography. Conventional radiography is limited in its capability to detect most intraabdominal pathology because most pathologic processes involve soft-tissue structures that are not well seen.

Pneumoperitoneum

Gastrointestinal perforation is diagnosed by seeing free intraperitoneal air under the diaphragm on an upright chest radiograph. Peptic ulcer perforation is associated with crack cocaine use. Esophageal or gastric perforation can be a complication of large-bore orogastric tube placement and forceful emesis induced by syrup of ipecac or alcohol intoxication. Esophageal and gastric perforation can also occur following the ingestion of caustic acids or alkalis.

Obstruction and Ileus

On the upright abdominal radiograph, both mechanical obstruction and adynamic ileus show air-fluid levels. In mechanical obstruction, air-fluid levels are seen at different heights and produce a "stepladder" appearance. Mechanical bowel obstruction can be caused by large intraluminal foreign bodies such as a body packer's packets or a medication bezoar. Adynamic ileus can complicate ingestions of opioids, anticholinergics, and tricyclic antidepressants.

Neurologic Complications

Imaging studies have revolutionized the diagnosis of CNS disorders. Some xenobiotics have a direct effect on the CNS, whereas with others, neurologic injury is an indirect sequela of the xenobiotic exposure caused by hypoxia, hypotension, hypertension, cerebral vasoconstriction, head trauma, or infection.

Emergency Head CT Scanning

An emergency noncontrast head CT scan is obtained to detect acute intracranial hemorrhage and focal brain lesions causing cerebral edema and mass effect. Patients with these lesions present with focal neurologic deficits, seizures, headache, or altered mental status. Toxicologic causes of intraparenchymal and subarachnoid hemorrhage include cocaine or other sympathomimetic xenobiotics.

Xenobiotic-Mediated Neurodegenerative Disorders

A number of xenobiotics directly damage brain tissue, which produces morphologic changes that are detectable with CT and MRI. Such changes include generalized atrophy, focal areas of neuronal loss, demyelinization, and cerebral edema.

Atrophy Ethanol is the most widely used neurotoxin. With long-term ethanol use, there is a widespread loss of neurons with resultant atrophy. Chronic toluene exposure (occupational and illicit use) also causes diffuse cerebral atrophy.

Focal Degenerative Lesions Carbon monoxide poisoning produces focal degenerative lesions in the brain. In about half of patients with severe neurologic dysfunction following carbon monoxide poisoning, CT scans show bilateral symmetric lucencies in the basal ganglia, particularly the globus

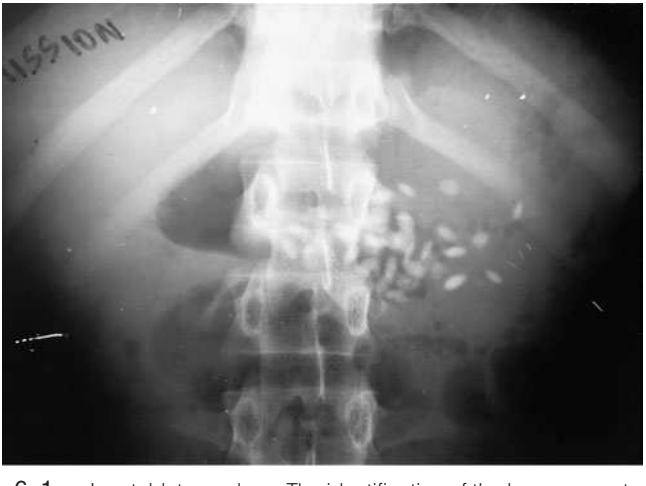
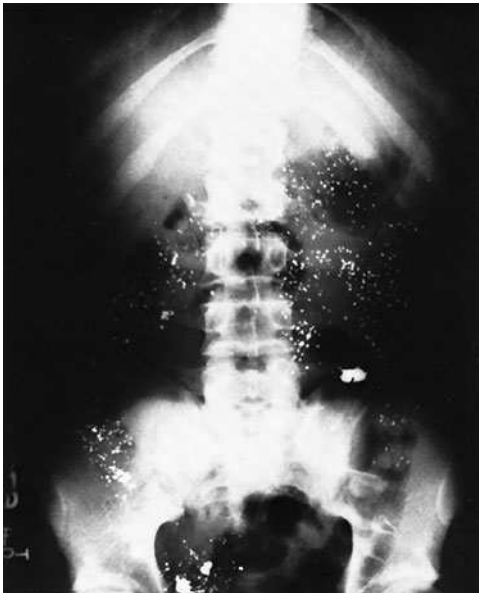
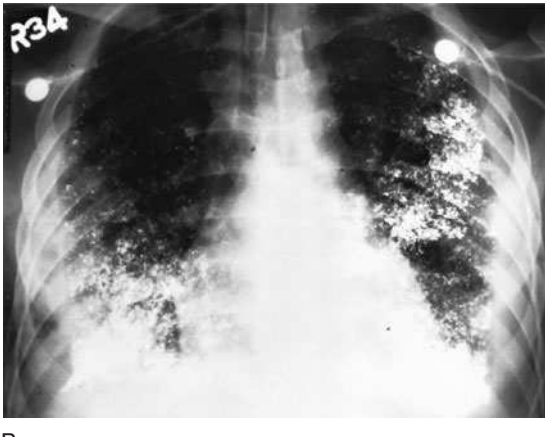


FIG. 6–1. Iron tablet overdose. The identification of the large amount of radiopaque tablets confirms the diagnosis in a patient with a suspected iron overdose and permits rough quantification of the amount ingested. *(Courtesy of the Toxicology Fellowship of the New York City Poison Control Center.)*

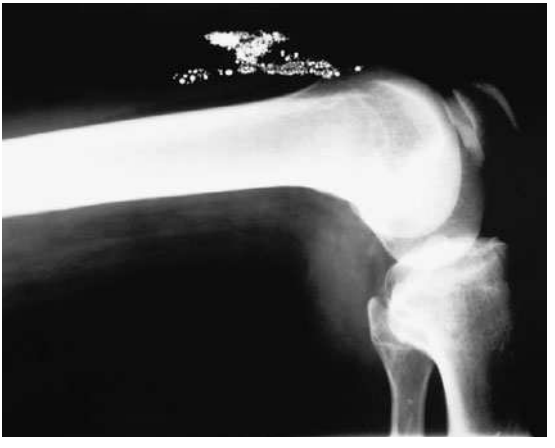


A



B

FIG. 6–2. Liquid elemental mercury exposures. **A.** Unintentional rupture of a Cantor intestinal tube distributed mercury throughout the bowel. *(Courtesy of Dr. Richard Lefleur, New York University.)* **B.** The chest radiograph in a patient following intravenous injection of elemental mercury showing metallic pulmonary embolism. The patient developed respiratory failure, pleural effusions, and uremia, and expired despite aggressive therapeutic interventions. *(Courtesy of Dr. N. John Stewart.) (continued)*



C

FIG. 6–2. *(continued.)* **C.** Subcutaneous injection of liquid elemental mercury is readily detected radiographically. Because mercury is systemically absorbed from subcutaneous tissues, it must be removed by surgical excision. *(Courtesy of the Toxicology Fellowship of the New York City Poison Control Center.)*

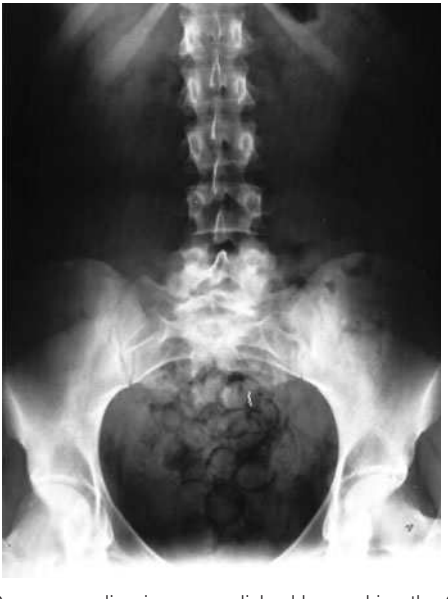


FIG. 6–3. Drug smuggling is accomplished by packing the GI tract with large numbers of manufactured well-sealed containers. The packets are visible in this patient because they are surrounded by a thin layer of air within the wall of the packet. *(Courtesy of Dr. Emil J. Balthazar, New York University.)*

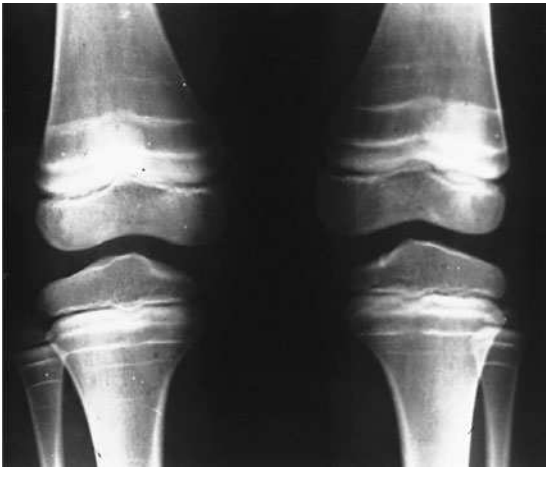


FIG. 6–4. A radiograph of the knees of a child with lead poisoning. The metaphyseal regions of the distal femur and proximal tibia have developed transverse bands representing bone growth abnormalities caused by lead toxicity. The multiplicity of lines implies repeated exposures to lead. *(Courtesy of Dr. Nancy Genieser, New York University.)*

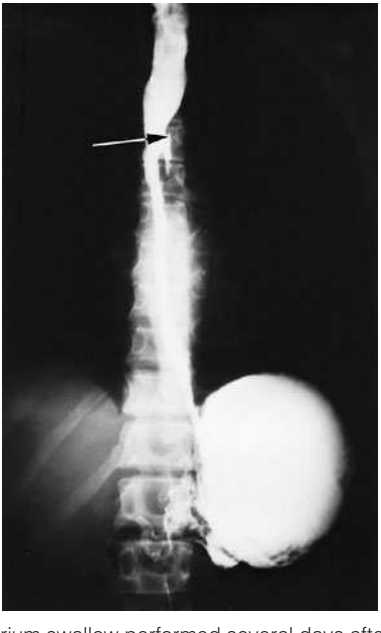


FIG. 6–5. A barium swallow performed several days after ingestion of liquid lyes shows intramural dissection and extravasation of barium with early stricture formation. *(Courtesy of Dr. Emil J. Balthazar, New York University.)*

pallidus. The basal ganglia are especially sensitive to hypoxic damage because of their limited blood supply and high metabolic requirements. Basal ganglion lucencies, white matter lesions, and atrophy are caused by other xenobiotics such as methanol, ethylene glycol, cyanide, hydrogen sulfide, inorganic and organic mercury, manganese, and heroin. Nontoxicologic disorders can also cause similar imaging abnormalities, including hypoxia, hypoglycemia, and infectious encephalitis.

Figures 6–1 to 6–5 show classic examples of the use of radiography in toxicology.

7 Laboratory Principles

Detecting the presence or measuring the concentration of both therapeutic and nontherapeutic xenobiotics is the primary activity of the medical toxicology laboratory. The unifying characteristic of the substances typically measured is their common presentation in patients with toxicologic emergencies, and the subsequent need for testing results within a relatively short time frame.

RECOMMENDATIONS FOR ROUTINELY AVAILABLE TOXICOLOGY TESTS

The recommendations in Table 7–1 were developed by the National Academy of Clinical Biochemists (NACB) from a consensus process involving clinical biochemists, medical toxicologists, forensic toxicologists, and emergency medicine physicians.

USING THE TOXICOLOGY LABORATORY

There are many reasons for toxicologic testing. The most common function is to confirm or exclude toxic exposures suspected from the history and physical examination. A laboratory result provides a level of confidence not otherwise readily obtained and may avert other unproductive diagnostic investigations driven by the desire for completeness and medical certainty. Testing increases diagnostic certainty in more than half of cases. In some instances, a diagnosis may be based primarily on the results of testing. This can be particularly important in poisonings with substances having delayed onset of clinical toxicity, such as acetaminophen, or in patients with ingestion of multiple substances. In these instances, characteristic clinical findings may not have yet developed at the time of presentation, or may be obscured or altered by the effects of coingestants.

Testing can provide two key parameters that will have a major impact on the clinical course, namely, the toxin involved and the intensity of the exposure. This information can assist in triage decisions, such as whether to admit a patient or to observe the individual for expectant discharge. Serum concentrations can facilitate decisions to employ specific antidotes or specific interventions to hasten elimination. Well-defined exposure information can also facilitate provision of optimum advice by poison centers, whose personnel do not have the ability to make decisions based on direct observation of the patient. Serum concentrations can be used to determine when to institute and terminate interventions such as hemodialysis or antidote administration, and can support the decision to transfer from intensive care or discharge from the hospital. Finally, positive findings for ethanol or drugs of abuse in trauma patients may serve as a risk marker for the likelihood of future trauma.

The confirmation of a clinical diagnosis of poisoning provides an important feedback function, whereby the physician may evaluate the diagnosis against a "gold standard." Another important benefit is reassurance; for example, reassurance that an unintentional ingestion did not result in absorption of a toxic amount of drug. Such reassurance can allow a physician to avoid spending excessive time with patients who are relatively stable. It can allow

TABLE 7–1. Toxicology Assays Recommended by the National Academy of Clinical Biochemists

Serum Assays, Quantitative	Urine Assays, Qualitative
Acetaminophen	Amphetamines
Carbamazepine	Barbiturates
Cooximetry (carboxyhemoglobin, methemoglobin, oxygen saturation)	Cocaine
Digoxin	Opiates
Ethanol	Propoxyphene
Iron (plus transferrin or unfilled iron-binding capacity)	Phencyclidine
Lithium	Tricyclic antidepressants
Phenobarbital	
Salicylate	
Theophylline	
Valproic acid	

Reprinted with permission from Wu AH, McKay C, Broussard LA, et al: National Academy of Clinical Biochemists laboratory medicine practice guidelines: Recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. *Clin Chem* 2003;49:357–379.

admissions to be made and interventions undertaken more confidently and efficiently than would be likely based solely on a clinical diagnosis. This can be especially beneficial in a setting where multiple cases are competing for the physician's attention.

Testing may also be indicated for medicolegal reasons. Diagnoses with legal implications should be established "beyond a reasonable doubt." Although testing for illicit drugs is often done for medical purposes, it is almost impossible to dissociate such testing from legal considerations. Documentation is also important in malevolent poisonings, intentional or unintentional child abuse involving therapeutic or illicit drugs, and pharmacologic elder abuse. Where test results may be used to document clear criminal activity, consideration should be given to having testing done in a forensic laboratory, maintaining full chain of custody.

The documentation function is also important outside the medicolegal arena. Results of testing in a central laboratory are almost invariably entered into the patient's medical record and can often provide definitive confirmation of a problem. Documentation has an additional importance that goes beyond the individual cases. Medical toxicology does not lend itself readily to experimental human investigation. Much of toxicologic knowledge is derived from experiments of nature, and recorded in case reports and case series. Hard data, such as drug concentrations, can serve as key quantitative variables in summarizing and correlating the data. That laboratory results can be reliably and, generally, easily found in the medical record, makes them particularly valuable in retrospective reviews. A related service that the toxicology laboratory may provide is testing in support of experimental investigations.

The key to optimum use of the toxicology laboratory is communication. This begins with learning the capabilities of the laboratory—what drugs are on its menus, which ones can be measured and which merely detected, what are anticipated turnaround times. For screening assays, one should know which drugs are routinely detected, which ones can be detected if specifically requested, and which ones cannot be detected, even when present at toxic concentrations.

A key item is learning which specimens are appropriate for the test requested. A general rule is that quantitative tests require serum (red stopper) or heparinized plasma (green stopper), but not ethylenediaminetetraacetic acid (EDTA) plasma (lavender stopper) or citrate plasma (light blue stopper). EDTA and citrate bind divalent cations that may serve as cofactors for enzymes used as reagents or labels in various assays. Additionally, liquid EDTA and citrate anticoagulants dilute the specimen. Serum separator tubes or plasma separator tubes, identifiable by the separator gel in the tube, should be avoided, as some drugs may diffuse into the gel, leading to falsely low results. A random, clean urine specimen is generally preferred for toxicology screens, as the higher drug concentrations usually found in urine can compensate for the lower sensitivity of the broadly focused screening techniques. A urine specimen of 20 mL is usually optimal. Requirements for all specimens may vary from laboratory to laboratory.

An important, and often overlooked, item of communication is specifying drugs that are particularly suspected when making a request for a screening test. This knowledge enables the laboratory to set up the tests for those drugs first, and possibly adjust the protocols to increase sensitivity or specificity. This may save an hour or more in the time needed for the laboratory to provide the critical information.

Consultation with the laboratory regarding puzzling cases or unusual needs can allow consensus on an effective and feasible testing strategy. The full capabilities of a toxicology laboratory are often not apparent from published lists of tests available. Most full-service laboratories devote substantial efforts to meeting reasonable requests, and provide consultations at no charge.

The laboratory should also be contacted whenever results are inconsistent with the clinical presentation. The most common causes for this are interferences and preanalytical errors. Analytical interference is caused by materials in the specimen that interfere with the measurement process, leading to falsely high or low results. For example, hemoglobin can interfere with a variety of spectrophotometric tests by absorbing the light used to make the measurement. Preanalytical errors are events that occur prior to laboratory analysis and produce incorrect or misleading results, such as mislabeling, specimen contamination by intravenous solutions, and incorrect collection time or technique. The laboratory is familiar with the common sources of these discrepancies. If the discrepancy is the result of laboratory error, it is critical that the laboratory be informed, so that steps can be taken to understand the source of the error and avoid a recurrence.

METHODS USED IN THE TOXICOLOGY LABORATORY

Table 7–2 compares the basic features of the methodologies used in the toxicology laboratory. Other methodologies include ion-selective electrode measurements of lithium, atomic absorption spectroscopy or inductively coupled plasma mass spectroscopy for lithium and heavy metals, and anodic stripping methods for heavy metals.

Spot Tests

These rely on the rapid reaction of a drug with a chemical reagent to produce a colored product; for example, the formation of a colored complex between salicylate and ferric ions.

TABLE 7–2. Relative Comparison of Toxicology Methods

Method	Sensitivity	Specificity	Quantitation	Analyte Range	Speed	Cost
Spot test	+	±	No	Few	Fast	$
Spectrochemical	+	+	Yes	Few	Medium	$
Immunoassay	++	++	Yes	Moderate	Medium	$$
TLC	+	++	No	Broad	Slow	$$
HPLC	++	++	Yes	Broad	Medium	$$
GC	++	++	Yes	Broad	Medium	$$
GC/MS	+++	+++	Yes	Broad	Slow	$$$
LC/MS/MS	+++	+++	Yes	Broad	Medium	$$$$

GC, gas chromatography; GC/MS, gas chromatography-mass spectroscopy; HPLC, high-performance liquid chromatography; LC/MS/MS, liquid chromatography-tandem mass spectroscopy; TLC, thin-layer chromatography.

Spectrochemical Tests

These rely on a chemical reaction to form a light-absorbing substance. They differ from simple spot tests in that the reaction conditions and reagent concentrations are carefully controlled and the amount of light absorbed is quantitatively measured at one or more specific wavelengths.

Immunoassays

The combination of high affinity and high selectivity make antibodies ideal assay reagents. There are two common types of immunoassays. In noncompetitive immunoassays, the analyte is sandwiched between two antibodies, each of which recognizes a different epitope on the analyte. In most commonly used immunoassays (competitive immunoassays), analyte from the patient's specimen competes for a limited number of antibody binding sites with a labeled version of the analyte provided in the reaction mixture (Fig. 7–1).

Chromatography

Chromatography encompasses several related techniques in which analyte specificity is achieved by physical separation. The unifying mechanism for separation is the partition of the analytes and other substances between a stationary phase and a moving phase (mobile phase). In most instances, the stationary phase consists of very fine particles arranged in a thin layer or enclosed within a column. The mobile phase flows through the spaces between the particles. Analytes are in a rapid equilibrium between solution in the mobile phase and adsorption to the surfaces of the particles. They move when in the mobile phase and stop when adsorbed to the stationary phase. Chromatography is a separation method and must be combined with a detection method to allow identification and measurement of the separated substances.

In thin-layer chromatography (TLC), the concentrated extracts are redissolved in a small amount of solvent and spotted onto a thin layer of silica gel that is supported on a glass or plastic plate, or embedded in a fiber matrix.

In the related technique of high-performance liquid chromatography (HPLC), the stationary phase is packed into a column and the mobile phase is pumped through under high pressure (Fig. 7–2). This allows good flow rates

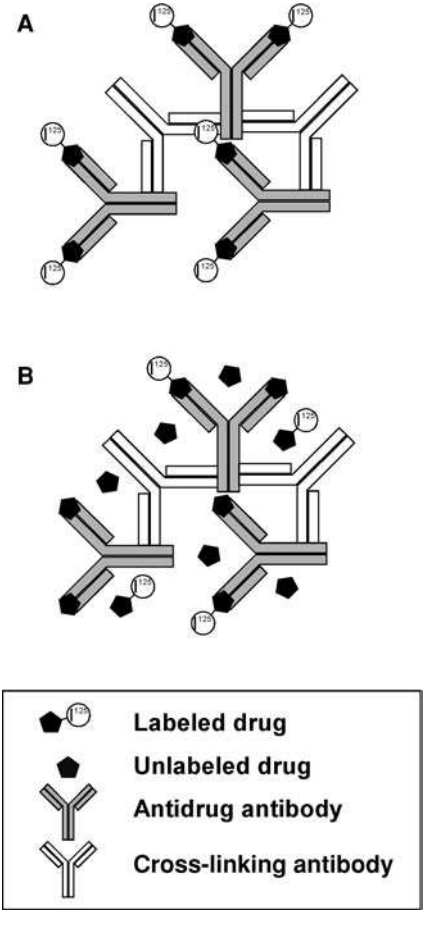


FIG. 7–1. Competitive radioimmunoassay. **A.** No drug from the specimen is present to displace the ^{125}I-labeled drug. Adding the cross-linking antibody precipitates the assay antibody, along with high amounts of bound radioactivity. **B.** Unlabeled drug in the specimen displaces some of the labeled drug. The displaced label is left in solution when the cross-linking antibody is added, resulting in less radioactivity in the precipitate.

to be achieved, even when solid phases with very small particle sizes are used. Smaller particle size increases surface area, decreases diffusion distances, and improves resolution, but the spaces between the particles are also smaller, increasing the resistance to flow. The use of high pressure and small particles allows better separations in a fraction of the time required for TLC.

Gas chromatography (GC) is similar in principle to HPLC, except that the moving phase is a gas, usually the inert gas helium or, occasionally, nitrogen. The low flow resistance of gas allows high flow rates that make possible substantially longer columns than are used in HPLC.

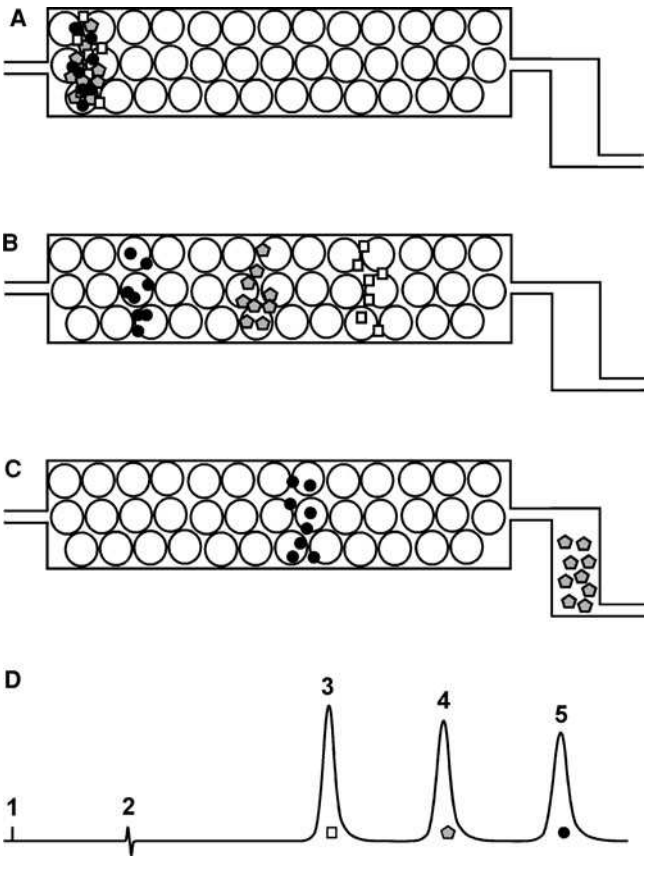


FIG. 7–2. High-performance liquid chromatography. HPLC is schematically shown. **A.** A mixture of three compounds is injected into a column with a reversed-phase packing. **B.** The compounds move through the column at characteristic speeds. The most hydrophilic compound (□) moves most quickly, whereas the most hydrophobic compound (●) moves most slowly. **C.** The compound of intermediate polarity (⬠) has reached the detection cell, where it absorbs light directed through the cell and generates a signal proportional to its concentration. **D.** Illustration of the HPLC tracing that might result: *1* indicates the time of injection. The artifact at *2* results when the injection solvent reaches the detector, and indicates the retention time of a completely unretained compound. The peaks at *3*, *4*, and *5* correspond to the separated compounds. For example, peak *4* might be amitriptyline; peak *3* might be the more polar metabolite, nortriptyline; and peak *5* could be the more hydrophobic internal standard *N*-ethylnortriptyline. Later-emerging peaks are typically wider and shorter, because of more time for diffusive forces to spread out the molecules.

Gas chromatography is limited to molecules that are reasonably volatile at temperatures below 572°F (300°C), above which the stationary phase may begin to break down. Two principal attributes of a molecule limit its volatility: its size and its ability to form hydrogen bonds. Molecules that form hydrogen bonds via amino, hydroxyl, and carboxylate moieties can be made more volatile by replacing hydrogens on oxygen and nitrogen atoms with a nonbonding, preferably large, substituent. (Large substituents sterically hinder access to the acceptor electron pairs on the nitrogen and oxygen atoms.) A number of derivatizing agents can be used to add appropriate substituents. The most common derivatives involve the trimethylsilyl (TMS) group. Although derivatization with TMS substantially increases the molecular weight, the resulting derivative is much more volatile as a result of the loss of hydrogen bonding.

A number of detectors are available for GC. The most common detector, particularly for packed columns, is the flame ionization detector. Organic molecules emerging from the column are burned, creating charged combustion intermediates that can be measured as a current. The mass spectrometer can serve as a highly sensitive GC detector and additionally possesses the ability to generate highly characteristic mass spectra from the compounds it is detecting. The mass spectrometer then uses electromagnetic filtering to direct only ions of a specified mass-to-charge (*m/z*) ratio to a detector. The mass spectrum of any compound is highly distinctive and usually unique.

QUANTITATIVE DRUG MEASUREMENTS

When properly used to guide dosing adjustments, drug concentration measurements improve medical outcomes. An essential requirement for interpretation of drug concentrations is that the relationship between drug concentrations and drug effects be known. The relationships between toxic concentrations and effects cannot be systematically studied in humans, and consequently are often incompletely defined. These relationships are largely inferred from data provided in overdose case reports and case series. For the toxicologist, drug concentrations are especially useful in two ways. For drugs whose toxicity is delayed or is clinically inapparent during the early phases of an overdose, drug concentrations may have substantial prognostic value. These concentrations may be used to make decisions regarding therapy or prognosis. Knowledge of the pharmacokinetics of a drug can substantially enhance the ability to draw meaningful conclusions from a measured concentration (Table 7–3).

For drugs that bind significantly to plasma proteins, it is the concentration of drug that is not bound to proteins (the free drug concentration) that is in equilibrium with concentrations at the site of action. Increasing the percentage of drug in free form results in stronger effects than would be predicted from the total drug concentration. Measurement of free drug concentrations can clarify such situations.

TOXICOLOGY SCREENING

A test unique to the toxicology laboratory is the toxicology screen, or "tox screen." Depending on the laboratory, this term may refer to a single comprehensive testing methodology, such as a TLC or GC, with the ability to detect multiple drugs. It may refer to a panel of individual tests, such as a drug abuse screen, or it may be a combination of broad spectrum and individual tests. (Table 7–4 suggests the components of a focused toxicology screen.) The wide-

TABLE 7–3. Factors That May Alter Concentration-Effect Relationships

Factor	Effect	Examples
Measurement during absorption phase	Underestimation of eventual effects	Sustained-release preparations; large ingestions of poorly soluble drugs (eg, salicylates); drugs that slow gastric emptying (eg, tricyclic antidepressants)
Measurement during distribution phase	Overestimation of effects	Lithium, digoxin, tricyclic antidepressants
Decreased binding to proteins	Underestimation of effects	Phenytoin
Saturation of binding proteins	Underestimation of effects	Salicylate, valproic acid
Binding by antidote	Variable	Digoxin/digoxin immune Fab

spread use of the term "tox screen" is unfortunate, as this wrongly implies for many physicians the availability of a test that can exclude poisoning as a diagnosis. Furthermore, a positive finding does not necessarily confirm a diagnosis of poisoning. For assays that detect only the presence of a drug, it is not possible to distinguish benign or therapeutic concentrations from toxic ones. Quantitative tests may falsely suggest toxicity when drug concentrations are measured during the distribution phase of the drug, which may extend for several hours with drugs like digoxin and lithium. Moreover, the phenomenon of tolerance may allow chronic drug users to be relatively unaffected by concentrations that would be quite toxic to a naive individual.

SPECIAL CONSIDERATIONS FOR DRUG-ABUSE SCREENING TESTS

Testing for drugs of abuse is a significant component of medical toxicology testing. Initial testing is usually done with a screening immunoassay. Positive results

TABLE 7–4. Components of a Focused Toxicology Screen

Serum Tests	Urine Tests
Acetaminophen	Cocaine metabolite
Ethanol	Opiates
Salicylates	Tricyclic antidepressants[a]
Tricyclic antidepressants (semiquantitative immunoassay)	
Consider including:	
Barbiturates	Amphetamines
Cooximetry[b]	Barbiturates[a]
Iron	Benzodiazepines
Lithium	Methadone
Theophylline	Phencyclidine
Valproic acid	Propoxyphene
Volatile alcohols[c]	
Other locally prevalent drugs	

[a]If not included in serum tests.
[b]Requires whole-blood specimen.
[c]Methanol, isopropanol (+ acetone).

may be confirmed by retesting using a nonimmunologic test, but this is frequently not done. (Drug-abuse testing for nonmedical reasons is generally considered to be forensic testing, and confirmation is considered mandatory in such circumstances.) The most commonly tested for drugs are amphetamines, cannabinoids, cocaine, opiates, and phencyclidine. These are often referred to as the NIDA 5, because they are the five drugs that were recommended for drug screening of federal employees by the National Institute on Drug Abuse (NIDA) in 1988. Drug-screening immunoassays are also frequently done for barbiturates and benzodiazepines, and less frequently for methadone and propoxyphene.

The use of specific cutoff concentrations is nearly universal. Test results are considered positive only when the concentration of drug in the specimen exceeds a predetermined threshold. This threshold should be set sufficiently high so that false-positive results because of analytic variability or because of crossreactivity are extremely infrequent. They should also be low enough to consistently give a positive result in persons who are using drugs. Cutoff concentrations used will vary with the drug or drug class under investigation. The use of cutoff values sometimes creates confusion, such as when a patient who is known to recently have used a drug has a negative result reported on a drug screen. In such instances, the drug is usually present, but at a concentration below the cutoff value.

Another widely used practice is the confirmation of positive screening results using an analytical methodology different from that used in the screen, such as an immunoassay screen followed by chromatographic confirmation. The possibility of simultaneous false-positive results by two distinct methods is quite low. The most common confirmatory method is gas chromatography-mass spectroscopy. The high specificity afforded by the combination of the retention time and the mass spectrum makes false-positive results extremely unlikely.

REGULATORY ISSUES AFFECTING TOXICOLOGY TESTING

Since 1992, medical laboratory testing has been governed by federal regulations (42 CFR part 405 *et seq*) issued under the authority of the Clinical Laboratory Improvement Amendments of 1988 (often referred to as CLIA-88 or simply CLIA). These regulations apply to all laboratory testing of human specimens for medical purposes, regardless of site. They include the universal requirement for possession of an appropriate certificate to perform even the simplest of tests. The remaining requirements depend on the complexity of the test. These regulations become important to the medical toxicologist whenever testing is done at the bedside, whether using spot tests or commercial point-of-care devices, such as dipsticks, glucose meters, and urine drug-screening devices.

The regulations divide testing into three categories: waived, moderate complexity, and high complexity. Waived tests include a number of specifically designated simple tests, including urine dipsticks, urine pregnancy tests, urine drug-screening immunoassay devices, and blood glucose measurements with a hand-held monitor. Most assays performed with commercial kits or devices are classified as belonging to the moderately complex category. There are substantial requirements for both moderate and highly complex testing, most of which simply represent good laboratory practice.

Breath tests for ethanol and carbon monoxide are not regulated by CLIA, because no human specimen is involved. However, such testing may be covered by state laws or by institutional or accrediting agency policies.

8 Techniques Used to Prevent Gastrointestinal Absorption

Gastrointestinal decontamination has remained one of the most controversial issues in medical toxicology for many years. It plays a central role in the initial management of the orally poisoned patient, and it is frequently the only treatment available in addition to necessary supportive care. As might be suspected, available studies fail to provide adequate guidance for the management of a patient who definitely has taken an unknown ingestion at an unknown time. Fortunately, in most cases there is either some component of the history or clinical presentation, such as vital signs, physical examination, and routine diagnostic studies (such as ECG and anion gap), that offers insight into the nature of the ingested xenobiotic.

Recommendations made by experts, clinicians, and authors for both theoretical and actual patients vary widely. These differences suggest that there is inadequate evidence available to produce a proper evidence-based answer for many of the decisions in question. Most of the clinical studies that provide evidence for consensus statements include limited numbers of xenobiotics and few life-threatening ingestions. Similarly, there are no studies for most drugs with modified release kinetics or for many new drugs. Thus, the clinician often must make decisions based on a philosophic approach (outlined below) and an understanding of specific principles rather than evidence. Subsequent Antidotes-in-Brief sections provide more information on the actual methods of decontamination.

GASTRIC EMPTYING

The principal theory governing gastric emptying is very simple: If a portion of xenobiotic can be removed prior to absorption, its potentially toxic effect should either be prevented or minimized. Multiple studies on gastric emptying clearly demonstrate that many patients can be successfully managed without aggressive gastric emptying. The clinical parameters listed in Table 8–1 help to identify those individuals for whom gastric emptying is usually *not* indicated based on a risk-to-benefit analysis. In contrast, for a small subset of patients (Table 8–1) gastric emptying may be indicated. A thorough understanding of this risk analysis is essential for every patient who ingests a xenobiotic.

Time is an important consideration because in order for gastric emptying to be beneficial, a consequential amount of xenobiotic must still be present in the stomach. Demographic studies have found that very few poisoned patients arrive at the hospital soon after an ingestion. Average times from ingestion to presentation in most studies are approximately three to four hours, with significant variations. This delay diminishes the likelihood of recovering large percentages of the xenobiotic from the stomach, unless patients have ingested a xenobiotic that slows gastric emptying rates. Recent data serve to highlight the arbitrary nature of this limitation. In a prospective study of 85 poisoned patients, gastric scintigraphy demonstrated markedly prolonged gastric emptying half-times and gastric hypomotility.

TABLE 8–1. Risk Assessment: When to Consider Gastric Emptying

Gastric Emptying Is Usually **Not** Indicated If[a]
Although the xenobiotic ingested is potentially toxic, the dose ingested is less than that expected to produce significant illness.
The ingested xenobiotic is well adsorbed by activated charcoal, and the amount ingested is not expected to exceed the adsorptive capacity of activated charcoal.
Significant spontaneous emesis has occurred.
The patient presents many hours postingestion and has minimal signs or symptoms of poisoning.
The ingested xenobiotic has a highly efficient antidote (such as acetaminophen).
Gastric Emptying May Be Indicated If[b]
There is reason to believe that, given the time of ingestion, a significant amount of the ingested xenobiotic is still present in the stomach.
The ingested xenobiotic is known to produce serious toxicity or the patient has obvious signs or symptoms of life-threatening toxicity.
The ingested xenobiotic is not adsorbed by activated charcoal.
Although the ingested xenobiotic is adsorbed by activated charcoal, the amount ingested exceeds the activated charcoal-to-xenobiotic ratio of 10:1 even with a double-standard dose of activated charcoal.
The patient has not had spontaneous emesis.
No highly effective specific antidote exists or alternative therapies (such as hemodialysis) pose a significant risk to the patient.

[a]Patients who fulfill these criteria can be decontaminated safely with activated charcoal alone or may require no decontamination at all.
[b]Patients who fulfill these criteria should be considered candidates for gastric emptying if there are no contraindications. For individuals who meet some of these criteria but who are judged not to be candidates for gastric emptying, single- or multiple-dose activated charcoal and/or whole-bowel irrigation should be considered.

The assessment continues with an evaluation for potential contraindications (Table 8–2). Regardless of the severity of the ingestion and other contributing factors, such as time, there must not be any contraindication to gastric emptying procedures. Because the demonstrable benefit of emptying is marginal at best, even a relative contraindication usually dictates that the procedure should not be attempted.

Once the decision to perform gastric emptying is made, the clinician must choose between the two available methods.

Orogastric Lavage

Many authors adopt the consensus approach that orogastric lavage should *not* be considered unless a patient has ingested a potentially life-threatening amount of a xenobiotic and the procedure can be undertaken within 60 minutes of ingestion. A synthesis of available data can be used to develop indications for orogastric lavage (Table 8–2). When deciding whether to actually perform orogastric lavage for a poisoned patient, these indications, contraindications, and potential adverse effects must be considered (see below). Table 8–3 summarizes the actual technique for orogastric lavage.

Adverse effects of orogastric lavage include injury to the airway, esophagus, and stomach. These injuries, as well as other well-known complications such as aspiration pneumonitis, emphasize that orogastric lavage is not risk

TABLE 8–2. Indications for and Contraindications to Orogastric Lavage

Indications
The benefits of gastric emptying outweigh the risks.
Contraindications
The patient does not meet criteria for gastric emptying (Table 8–1).
The patient has lost or will likely lose his/her airway protective reflexes and has not been intubated. (Once intubated, orogastric lavage can be performed if otherwise indicated.)
Ingestion of an alkaline caustic.
Ingestion of a foreign body (such as a drug packet).
Ingestion of a xenobiotic with a high aspiration potential (such as a hydrocarbon) in the absence of endotracheal intubation.
The patient is at risk of hemorrhage or gastrointestinal perforation because of underlying pathology, recent surgery, or other medical condition that could be further compromised by the use of orogastric lavage.
Ingestion of a xenobiotic in a form known to be too large to fit into the lumen of the lavage tube (such as many modified-release preparations).

free and should only be considered based on the rigorous indications for gastric emptying as listed above.

Syrup of Ipecac

Although many animal and human studies show a reduction in drug concentrations with induced emesis, no clinical benefit for this technique has ever been proven. Furthermore, in view of the benefits of activated charcoal and the impor-

TABLE 8–3. The Technique of Performing Orogastric Lavage

Select the correct tube size

Adults/adolescents: 36–40 French

Children: 22–28 French

Procedure

1. If there is potential airway compromise, endotracheal or nasotracheal intubation should precede orogastric lavage.
2. The patient should be kept in the left-lateral decubitus position. Because the pylorus points upward in this orientation, this positioning theoretically helps prevent the xenobiotic from passing through the pylorus during the procedure.
3. Prior to insertion, the proper length of tubing to be passed should be measured and marked on the tube. The length should allow the most proximal tube opening to be passed beyond the lower esophageal sphincter.
4. After the tube is inserted, it is essential to confirm that the distal end of the tube is in the stomach.
5. Withdraw any material present in the stomach and consider the immediate instillation of activated charcoal for large ingestions of xenobiotics known to be adsorbed by activated charcoal.
6. Via a funnel (or lavage syringe) instill in an adult 250 mL aliquots of a room-temperature saline lavage solution. In children, aliquots should be 10–15 mL/kg to a maximum of 250 mL.
7. Orogastric lavage should continue for at least several liters in an adult and for at least 0.5–1 L in a child or until no particulate matter returns and the effluent lavage solution is clear.
8. Following orogastric lavage, the same tube should be used to instill activated charcoal, if indicated.

TABLE 8–4. Indications and Contraindications for Syrup of Ipecac

Indications
Orogastric lavage cannot be performed or is contraindicated because of the size of the xenobiotic formulation.
The history and/or physical examination suggest that there is likely to be a clinically significant amount of xenobiotic remaining in the stomach.
The benefits of gastric emptying outweigh the risks from the contraindications.
Contraindications
The patient does not meet criteria for gastric emptying (Table 8–1).
Either activated charcoal or another oral agent is expected to be necessary in the next few hours.
Airway protective reflexes might be lost within the next 30–60 minutes.
Ingestion of a caustic.
Ingestion of a foreign body such as a drug packet or sharp item.
Ingestion of a xenobiotic with a high aspiration potential such as a hydrocarbon.
The patient is younger than 6 months of age, elderly, or debilitated.
The patient has a premorbid condition that would be compromised by vomiting.

tance of minimizing any delay in its administration, syrup of ipecac should not be used because it delays the administration of activated charcoal, as well as any other oral treatment. Given the lack of evidence demonstrating a clinically meaningful benefit of induced emesis *and* its significant contraindications, syrup of ipecac in the emergency department and at home should no longer be considered a routine part of management (Table 8–4). However, there still may be an extremely limited role for ipecac-induced emesis (Antidotes in Brief: Syrup of Ipecac).

PREVENTION OF XENOBIOTIC ABSORPTION

Activated Charcoal

Activated charcoal has long been recognized as an effective method for reducing the systemic absorption of many xenobiotics. For certain xenobiotics it also acts to enhance elimination through interruption of either the enterohepatic or enteroenteric cycle. Activated charcoal is the single most useful therapy in the management of patients with acute oral overdoses. Like other methods of gastrointestinal decontamination, there is a lack of sound evidence of its benefits as defined by clinically meaningful endpoints. It is generally accepted that unless there is a reason to suspect that a significant amount of xenobiotic is in the gut, and either airway protective reflexes are intact (and expected to remain so) or the patient's airway has been protected, the administration of activated charcoal is contraindicated.

Based on available data from in vivo and in vitro studies, the actual recommended dosing regimen for activated charcoal varies: 25–100 g in adults (1 g/kg body weight), and 0.5–1 g/kg body weight in children. These recommendations are generally based more on activated charcoal tolerance than on efficacy. When a calculation of a 10:1 activated charcoal-to-drug ratio exceeds these recommendations, either gastric emptying or multiple-dose activated charcoal (MDAC) therapy should be considered (Table 8–5).

Multiple-Dose Activated Charcoal

Multiple-dose activated charcoal is typically defined as more than two sequential doses of activated charcoal. In many cases, the actual number of

TABLE 8–5. Indications and Contraindications for Single-Dose Activated Charcoal Therapy without Gastric Emptying

Indications
Ingestion of a toxic amount of a xenobiotic that is known to be adsorbed by activated charcoal
The ingestion has occurred within a time frame amenable to adsorption by activated charcoal or clinical factors are present that suggest that not all of the xenobiotic has already been systemically absorbed
Contraindications
Activated charcoal is known not to adsorb a clinically meaningful amount of the ingested xenobiotic
Airway protective reflexes are absent or expected to be lost and the patient is not intubated
Gastrointestinal perforation is likely as in cases of caustic ingestions
Therapy may increase the risk and severity of aspiration, such as in the presence of hydrocarbons with a high aspiration potential
Endoscopy will be an essential diagnostic modality (acid or alkaline caustics)

doses administered can be substantially greater. This technique serves two purposes: (a) to prevent ongoing absorption of a xenobiotic that persists in the gastrointestinal tract (usually in the form of a modified-release preparation), and (b) to enhance elimination by either disrupting enterohepatic recirculation or by "gut-dialysis" (enteroenteric recirculation).

Like single-dose activated charcoal, MDAC can produce emesis with subsequent pulmonary aspiration of gastric contents. It is intuitive that these risks are greater with multiple-dose than with single-dose therapy. Table 8–6 summarizes the indications and contraindications for MDAC therapy. Because the optimal doses and intervals for repeated doses of activated charcoal are not established, recommendations are based more on amounts that can be tolerated, rather than on amounts that might be considered pharmacologically appropriate. Table 8–7 lists typical dosing regimens. Larger doses and shorter intervals should be used for patients with more severe toxicity. It is reasonable to base end points on either the patient's clinical condition or xenobiotic concentrations when they are easily measured.

WHOLE-BOWEL IRRIGATION

Whole-bowel irrigation (WBI) represents a method of flushing the gastrointestinal tract in an attempt to prevent further absorption of xenobiot-

TABLE 8–6. Indications and Contraindications for Multiple-Dose Activated Charcoal Therapy

Indications
Ingestion of a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline
Ingestion of a life-threatening amount of another xenobiotic that undergoes enterohepatic or enteroenteric recirculation that is adsorbed to activated charcoal
Ingestion of a significant amount of any slowly released xenobiotic, or of a xenobiotic known to form concretions or bezoars
Contraindications
Any contraindication to single-dose activated charcoal
The presence of an ileus or other causes of diminished peristalsis

TABLE 8–7. Technique of Administering Multiple-Dose Activated Charcoal Therapy

Initial dose orally or via orogastric or nasogastric tube

Adults and children: 1 g/kg of body weight or a 10:1 ratio of activated charcoal-to-xenobiotic, whichever is greater. Following massive ingestions, 2 g/kg of body weight might be indicated, if such a large dose can be easily administered and tolerated.

Repeat doses orally or via orogastric or nasogastric tube

Adults and children: 0.25–0.5 g/kg of body weight every 1–6 hours, in accordance with the dose and dosage form of xenobiotic ingested (larger doses or shorter dosing intervals occasionally may be indicated).

Procedure

1. Add 8 parts of water to the selected amount of powdered form. All formulations, including prepacked slurries, should be shaken well for at least 1 minute to form a transiently stable suspension prior to drinking or instillation via orogastric or nasogastric tube.
2. Activated charcoal can be administered with a cathartic, *for the first dose only*, when indicated, but cathartics should never be administered routinely and never be repeated with subsequent doses of activated charcoal.
3. If the patient vomits the dose of activated charcoal, it should be repeated. Smaller, more frequent doses or continuous nasogastric administration may be better tolerated. An antiemetic may be needed.
4. If a nasogastric or orogastric tube is used for MDAC administration, time should be allowed for the last dose to pass through the stomach before removing the tube. Suctioning the tube itself prior to removal may prevent subsequent charcoal aspiration.

ics. This is achieved through the oral or nasogastric administration of large amounts of an osmotically balanced polyethylene glycol electrolyte lavage solution (PEG-ELS). When experimental, theoretical, and anecdotal human experience is considered, the use of WBI with PEG-ELS can be supported for patients with potentially toxic ingestions of sustained-release pharmaceuticals and iron. Other theoretical indications include the ingestion of large amounts of a xenobiotic where morbidity is expected to be high and absorption slow, the ingested xenobiotic is not adsorbed to activated charcoal, and other methods of gastrointestinal decontamination are unlikely to be either safe or beneficial. The removal of packets of illicit drugs (eg, from body-packers) can be considered a unique indication for WBI.

The contraindications for WBI are more clearly defined. This technique cannot be applied safely if the gastrointestinal tract is not intact, there are signs of ileus or obstruction, significant gastrointestinal hemorrhage, or in patients with inadequate airway protection, uncontrolled vomiting or consequential hemodynamic instability that compromise gastrointestinal function or integrity. Finally, the combination of WBI and activated charcoal decreases the adsorption of xenobiotics to activated charcoal, especially when the WBI solution is premixed with activated charcoal. Activated charcoal seems to be most efficacious if administered before initiating WBI.

The indications for WBI must, at the present time, remain theoretical, as the only support for the efficacy of this procedure comes from surrogate markers and anecdotal experience. Table 8–8 summarizes the indications and the contraindications to WBI.

TABLE 8–8. Indications and Contraindications for Whole-Bowel Irrigation

Indications
Ingestion of a toxic amount of a xenobiotic that is not adsorbed to activated charcoal when other methods of gastrointestinal decontamination are not possible or not efficacious
Removal of packets of illicit drugs (eg, from body-packers)
Contraindications
Airway protective reflexes are absent or expected to become so in a patient who has not been intubated
Gastrointestinal tract is not intact
Signs of ileus obstruction, significant gastrointestinal hemorrhage, or hemodynamic instability that might compromise gastrointestinal motility
Persistent vomiting
Signs of leakage from illicit cocaine packets (indication for surgical removal)

CATHARTICS

At the present time there seems to be no indication for the *routine* use of cathartics as a method of either limiting absorption or enhancing elimination. A single dose can be given as an adjunct to activated charcoal therapy when there are no contraindications, and constipation or an increased gastrointestinal transit time is expected.

SURGERY AND ENDOSCOPY

Surgery and endoscopy are occasionally indicated for decontamination of poisoned patients. As might be expected, there are no controlled studies, and potential indications are based largely on case reports and case series. A prospective uncontrolled series of 50 patients with cocaine packet ingestion was collected more than 20 years ago. The patients were conservatively observed and only underwent surgery if there were signs of leakage or mechanical bowel obstruction. As most packages do not spontaneously rupture, mechanical obstruction was the most common reason for surgery. A few case reports have presented mixed results for the endoscopic removal of drug packets from the stomach. At present, this method is not generally recommended because of the potential for packet rupture. However, under exceptional circumstances there is certainly a precedent for attempting this procedure in a highly controlled setting such as an ICU or operating room.

In rare cases of massive iron overdoses where emesis, orogastric lavage, and gastroscopy had failed, gastrotomy was performed. The significant clinical improvement and postoperative recovery indicated that the surgery in these particular cases was the correct approach.

Syrup of Ipecac

The role of syrup of ipecac has changed dramatically in the last decade. A critical evaluation of animal, volunteer, and a limited number of clinical studies suggest that ipecac administration, once the mainstay of poison management for children and adults, should be reserved for a few selected circumstances rather than administered on a routine basis. The rationale for this change is based on the facts that (a) most poisonings in children are benign; (b) many adults overdose with xenobiotics that rapidly cause an altered mental status which constitutes a contraindication to the administration of ipecac; and (c) ipecac-induced vomiting may be delayed and/or persistent, thereby resulting in a delay in the administration of activated charcoal.

PHARMACOLOGY

Ipecac is derived from the dried rhizome and roots of plants found in Brazil belonging to the family Rubiaceae, such as *Cephaelis acuminata* and *Cephaelis ipecacuanha*. Cephaeline and emetine are the two alkaloids largely responsible for the production of nausea and vomiting, with cephaeline being the more potent. Each 15-mL dose of the syrup of ipecac contains 16–21 mg of cephaeline and 6.4–21 mg of emetine, resulting in variable cephaeline-to-emetine ratios. After administration to volunteers, peak plasma concentrations of the alkaloids were reached by one hour and were undetectable at six hours. Only 2% of the total amount of alkaloids in the ipecac were excreted in the urine within 48 hours, and alkaloids remained detectable in the urine for at least two weeks.

Syrup of ipecac induces vomiting both by local activation of peripheral emetic sensory receptors in the proximal small intestine, and by central stimulation of the chemoreceptor trigger zone. Serotonin$_3$ (5-HT$_3$) receptors mediate the nausea and vomiting produced by syrup of ipecac by both mechanisms.

Nearly 90% of children given syrup of ipecac vomit within 30 minutes (mean: 18.7 minutes). The onset of emesis following syrup of ipecac administration does not appear to be affected by fluid administration before or after syrup of ipecac, by the temperature of the fluids, or by gentle patient motion or walking. The average number of episodes of vomiting following syrup of ipecac administration is three, with a range of one to eight, and the duration of vomiting averages 23–60 minutes.

VOLUNTEER STUDIES

Numerous studies support the concept that the sooner syrup of ipecac is administered after ingestion, the greater the amount of the ingested substance that will be recovered. The decrease in the amount of substance absorbed varies from study to study because of differences in study design, including time to initiation of the various techniques and the particular substance or marker used to assess efficacy. Values on the order of 33% reduction are commonly reported, but vary widely depending on xenobiotic choice, timing of ipecac administration, and individual variability.

OVERDOSE PATIENTS

Forty self-poisoned patients were each given 20 radiopaque pellets on admission and randomized immediately to therapy with either orogastric lavage or

syrup of ipecac-induced emesis. Approximately 45% of the pellets were removed in both the orogastric lavage and the syrup of ipecac groups. Two patients in the lavage group and one in the syrup of ipecac group had 100% of the pellets removed, and two patients in the lavage group had no pellets removed.

OUTCOME STUDIES

A large emergency department (ED) study addressed whether gastric emptying with either syrup of ipecac followed by activated charcoal or orogastric lavage followed by activated charcoal was more effective than activated charcoal alone in overdosed patients. Syrup of ipecac did not affect the outcome in patients who arrived awake and alert. Several subsequent studies failed to show a benefit of ipecac-induced emesis before activated charcoal administration compared with the administration of activated charcoal alone. Furthermore, pulmonary aspiration was more common in patients who had the combined regimen. A study using the poison center database determined that home use of syrup of ipecac did not reduce the rate of ED referrals.

INDICATIONS

Most authorities agree with the American Academy of Pediatrics statement that syrup of ipecac should no longer be used routinely. Only a few groups of patients are considered appropriate candidates for the use of the syrup of ipecac, including those who (a) overdose on xenobiotics that do not cause a rapid change in mental status, such as acetaminophen or salicylates; (b) consume massive amounts of a xenobiotic that may exceed the binding capacity of activated charcoal, such as salicylates; and (c) ingest a xenobiotic not adsorbed to activated charcoal, such as lithium. Under these circumstances, if the presence of unabsorbed drug in the stomach remains a potential problem, then the use of syrup of ipecac *might* be appropriate in *rare* instances when weighed against the utility of activated charcoal or whole-bowel irrigation with PEG-ELS. The time frame for this decision is usually within one to two hours following ingestion.

CONTRAINDICATIONS

Syrup of ipecac should not be administered to patients who have ingested acids or alkalis, are younger than six months of age, are expected to deteriorate rapidly, have a depressed mental status, have a compromised gag reflex, have ingested objects such as batteries or sharps, or have a need for rapid gastrointestinal evacuation to prevent absorption. Syrup of ipecac should not be administered to those for whom the hazards of vomiting and aspiration of the ingested substance outweigh the risks associated with systemic absorption (eg, hydrocarbons), those who have significant prior vomiting, or those for whom vomiting will delay administration of an oral antidote, or to those with a hemorrhagic diathesis, or a nontoxic ingestion, or when toxin is no longer expected to be in the stomach.

ADVERSE EFFECTS

The most common problem associated with induced emesis is pulmonary aspiration of gastric contents. Uncommon problems that have occurred after therapeutic doses of syrup of ipecac include Mallory-Weiss esophageal tear; herniation of the stomach into the left chest in a child who had a previously

unrecognized underlying congenital defect of the diaphragm; intracerebral hemorrhage; pneumomediastinum; and vagally mediated bradycardia.

Chronic use of frequent doses of syrup of ipecac results in muscle weakness and congestive cardiomyopathy. Abuse can be documented by demonstrating emetine in the urine.

DOSAGE AND ADMINISTRATION

The dose of syrup of ipecac is 15 mL in children 1–12 years old and 30 mL in older children and adults. If vomiting does not ensue after the first dose, the same dose may be repeated once in 20–30 minutes. For children 6–12 months of age, ipecac use should be limited to a maximum single dose of 10 mL.

Activated Charcoal

Activated charcoal (AC), a fine, black, odorless powder, has been recognized for almost two centuries as an effective adsorbent of many substances. The current debate regarding the role of AC in poison management involves reconciling evidence-based studies in volunteers and small numbers of heterogeneous overdosed patients with clinical experience. AC should be considered for administration to a poisoned or overdosed patient following a risk-to-benefit assessment for the substance presumably ingested, for the circumstances of the exposure, and for the particular patient.

ADSORPTION: MECHANISMS AND CONSIDERATIONS

AC is produced in a two-step process beginning with the pyrolysis of various carbonaceous materials such as wood, coconut, petroleum, or peat. This processing is followed by treatment at high temperatures with a variety of oxidizing (activating) agents, such as steam or carbon dioxide, to increase the adsorptive capacity through the formation of an internal matrix of pores, resulting in a huge surface area. The rate of adsorption depends on external surface area, whereas the adsorptive capacity is dependent on the far larger internal surface area. The adsorptive capacity can be modified by altering the size of the pores. Current AC products have pore sizes that range from 10–1000 angstroms (Å) with most of the internal surface area created by the summation of 10–20 Å-sized pores. Most drugs are of moderate molecular weight (100–800 daltons) and adsorb well to pores in the range of 10–20 Å. Adsorption begins within about 1 minute of administration of AC, but may not reach equilibrium for 10–25 minutes.

The actual adsorption of a xenobiotic by activated charcoal relies on hydrogen bonding, ion–ion, dipole, and van der Waals forces, suggesting that most xenobiotics are best adsorbed by activated charcoal in their dissolved, nonionized form. Strongly ionized and dissociated salts, such as sodium chloride or potassium chloride, are not adsorbed, whereas nonionized or weakly dissociated salts like iodine and mercuric chloride, respectively, are adsorbed. Desorption (xenobiotic dissociation from activated charcoal) may occur, especially for weak acids, as the charcoal–xenobiotic complex passes from the stomach through the intestine and as the pH changes from acidic to basic.

AC decreases the systemic absorption of most xenobiotics, including, acetaminophen, aspirin, barbiturates, cyclic antidepressants, glutethimide, phenytoin, theophylline, and most inorganic and organic materials. Notable xenobiotics not amenable to AC are the alcohols, strong acids and alkalis, iron, lithium, magnesium, and potassium. Although the binding of AC to cyanide is less than 4%, the toxic dose is small and 50 g of AC would theoretically be able to bind more than 10 lethal doses of potassium cyanide.

The clinical efficacy of administered AC is also inversely related to the time elapsed following ingestion of the substance to be adsorbed and depends largely on the rate of absorption of the xenobiotic. For example, early administration is much more important with rapidly absorbed xenobiotics. In this situation, AC functions to prevent the absorption of xenobiotic into the body by achieving rapid adsorption in the GI tract. Once a xenobiotic is systemi-

cally absorbed or parenterally administered, AC may still enhance elimination through a mechanism referred to as gastrointestinal or gut dialysis. This is accomplished with multiple doses of AC and is discussed below.

INDICATIONS

AC should not be administered routinely to all overdosed patients. Single-dose AC should be administered to patients only when a xenobiotic is still expected to be available for adsorption in the GI tract and the benefit of its use outweighs the risk. Additionally, when the ingestion is known, the xenobiotic must be adsorbed to AC.

CONTRAINDICATIONS

Contraindications to AC include potential GI perforation and the need for endoscopic visualization, as may be the case with caustic ingestion. It is imperative that the patient's airway be assessed prior to administration to reduce the likelihood of aspiration pneumonitis. When the potential for airway compromise is substantial, oral AC should be withheld until a decision about airway protection is made. Other considerations that must be made prior to the administration of AC are the determination of normal gastrointestinal motility, normal bowel sounds, and a normal abdominal examination without distension or signs of an acute abdomen. If bowel function is compromised, the stomach should be decompressed to decrease the risk of subsequent vomiting and aspiration prior to administration of AC.

DOSING AND ADMINISTRATION

The optimal dose of AC is unknown. However, most authorities recommend a dose of AC of 1 g/kg body weight when the amount of xenobiotic is unknown, or when known in a 10:1 ratio of AC to drug, up to an amount that is safely administered. AC that is not premixed is best administered as a slurry in a 1:8 ratio of AC to suitable liquid, such as water or cola. Using cold cola may offer improved palatability without decreasing efficacy.

ADVERSE EFFECTS

The use of AC is relatively safe, although vomiting (especially after rapid administration), constipation, and diarrhea frequently occur following its administration. Constipation and diarrhea are more likely to result from the ingestion itself than from the AC. Serious adverse effects of AC include the complications that may result from the pulmonary aspiration of AC with or without gastric contents, peritonitis from spillage of AC into the peritoneum from gastrointestinal perforation, and intestinal obstruction and pseudo-obstruction, especially following repeated doses of AC in the presence of either dehydration or prior bowel adhesions.

THE USE OF ACTIVATED CHARCOAL WITH CATHARTICS AND WHOLE-BOWEL IRRIGATION

Cathartics are often used with AC, however the evidence suggests that the efficacy of AC alone is comparable to AC plus a single dose of cathartic (sorbitol or magnesium citrate). If a cathartic is used, it should be used only once, as repeated doses of magnesium-containing cathartics are associated with hy-

permagnesemia, and repeated doses of any cathartic can be associated with severe fluid and electrolyte disorders. Whole-bowel irrigation with PEG-ELS may significantly decrease the in vitro and in vivo adsorptive capacity of AC, depending on the individual xenobiotic and the formulation. The most likely explanation is competition with the charcoal surface for solute adsorption.

MULTIPLE-DOSE ACTIVATED CHARCOAL

Multiple-dose activated charcoal (MDAC) has two mechanisms of action: (a) to prevent the absorption of xenobiotics that are slowly absorbed from the GI tract, and (b) to enhance the elimination of suitable xenobiotics that have already been absorbed. MDAC decreases xenobiotic absorption when large amounts of xenobiotics are ingested and dissolution is delayed (eg, masses, bezoars), when drug formulations exhibit a delayed or prolonged release phase (eg, enteric coated, sustained release), or when reabsorption can be prevented (eg, enterohepatic circulation of either active xenobiotic, active metabolites, or conjugated xenobiotic hydrolyzed by gut bacteria to active xenobiotic).

Experimental Studies

Xenobiotics with the longest intrinsic plasma half-lives demonstrate the greatest percent reduction in plasma half-life when MDAC is used. Additional factors may include volume of distribution, distribution half-life, and protein binding. The benefits of MDAC undoubtedly depend on a number of other patient variables and xenobiotic exposure characteristics.

Overdose Studies

The most compelling demonstration of the benefits of MDAC in the overdose setting comes from a single study of patients with severe cardiac toxicity caused by intentional overdose with yellow oleander seeds. An initial dose of 50 g of AC was administered to all patients who were then randomized to 50 g of AC every six hours for three days or placebo. There were statistically fewer deaths and fewer life-threatening cardiac dysrhythmias in the MDAC group.

Administration of MDAC

An initial loading dose of AC should be administered as described above. The correct dose and interval for subsequent doses of AC is best tailored to the amount and dosage form of the xenobiotic ingested, the severity of the overdose, the potential lethality of the xenobiotic, and the patient's ability to tolerate AC. Benefit should always be weighed against risk. Reported doses of AC for multiple dosing have varied considerably, ranging from 0.25–0.5 g/kg body weight every one to six hours, to 20–60 g for adults every one, two, four, or six hours. There is some evidence that the total dose administered may be more important than the frequency of administration. We consider a dose of 0.5 g/kg body weight every 2–4 hours for up to 12 hours to be an appropriate regimen in most circumstances.

Whole-Bowel Irrigation and Other Intestinal Evacuants

Whole-bowel irrigation (WBI) is the most effective process for evacuating the intestinal tract in poisoned patients. This technique is typically accomplished utilizing polyethylene glycol 3350 (PEG) and an added electrolyte lavage solution (ELS).

MECHANISM OF ACTION

Polyethylene glycol is a nonabsorbable, isoosmotic indigestible xenobiotic. It remains in the colon, and together with the water diluent, is evacuated, resulting in WBI without producing flatus and cramps. Electrolytes are added to limit electrolyte and fluid shifts. Many studies of WBI using PEG-ELS demonstrate patient acceptance, effectiveness, and safety when used for bowel preparation.

GASTROINTESTINAL EVACUATION AND POISON MANAGEMENT

Cathartics should not be used routinely in the management of overdosed patients. Although theoretical advantages of cathartics are suggested from their ability to decrease constipation, hasten the delivery of activated charcoal (AC) to the small intestine, and propel unabsorbed xenobiotics out of the GI tract, these advantages have never been demonstrated clinically. In fact, when the efficacy of a single dose of AC alone is compared with that of AC plus a single dose of cathartic, results are widely disparate.

In contrast, WBI with PEG-ELS is currently advocated to hasten the elimination of poorly absorbed xenobiotics or sustained-release medications before they can be absorbed. This approach is theoretically sound, and also lacks the potential for the fluid and electrolyte complications associated with cathartics. Unfortunately, evidence of efficacy is limited to anecdotal case reports and volunteer studies.

There are reports of successful use of WBI in the management of overdoses of iron, sustained-release theophylline, sustained-release verapamil, zinc sulfate, lead, mercuric oxide powder, arsenic-containing herbicide, delayed-release fenfluramine, and for body packers.

ADVERSE EFFECTS OF WBI

Adverse effects resulting from the use of WBI with PEG-ELS include vomiting, particularly following rapid administration, abdominal bloating, fullness, cramping, flatulence, and pruritus ani. Slow or low-volume administration of PEG-ELS may also result in sodium absorption.

CONTRAINDICATIONS

Contraindications to WBI include prior, current, or anticipated diarrhea; volume depletion; significant gastrointestinal pathology or dysfunction, such as ileus, perforation, colitis, toxic megacolon, hemorrhage and obstruction; an unprotected or compromised airway; and hemodynamic instability.

DOSING AND ADMINISTRATION

The recommended dose of WBI with PEG-ELS solutions is 0.5 L/h or 25 mL/kg/h for small children and 1.5–2 L/h or 20–30 mL/min for adolescents and adults. WBI solution may be administered orally or through a nasogastric tube for four to six hours or until the rectal effluent becomes clear. If the xenobiotic being removed is radiopaque a diagnostic imaging technique demonstrating the absence of the xenobiotic may serve as a reasonable clinical end point. An antiemetic, such as metoclopramide or a serotonin antagonist, may be required for the treatment of nausea or vomiting.

9 Pharmacokinetic and Toxicokinetic Principles

Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion of drugs. Mathematical models and equations are used to describe and to predict this behavior. *Pharmacodynamics* is the term used to describe an investigation of the relationship of drug concentration to clinical effect. *Toxicokinetics*, which is analogous to pharmacokinetics, is the study of the absorption, distribution, metabolism, and excretion of a xenobiotic under circumstances that produce toxicity or excessive exposure. *Toxicodynamics*, which is analogous to pharmacodynamics, is the study of the relationship of toxic concentrations of xenobiotics to clinical effect. *Xenobiotics* are all substances that are foreign to the body.

Despite confounding and individual variability, toxicokinetic principles can be applied to overdose situations to facilitate our understanding and to make certain predictions. These principles can be used to help evaluate whether a certain antidote or extracorporeal removal method is appropriate for use, when the serum concentration might be expected to drop into the therapeutic range (if such a range exists), what ingested dose might be considered potentially toxic, what the onset and duration of toxicity might be, and what the importance of a serum concentration is. While considering all these factors, the clinical status of the patient is paramount, and mathematical formulas and equations can never substitute for evaluating the patient.

ABSORPTION

Absorption is the process by which a xenobiotic enters the body. Both the rate (k_a) and extent of absorption (F) are measurable and important determinants of toxicity. The rate of absorption often predicts the onset of action, whereas the extent of absorption (*bioavailability*) often predicts the intensity of the effect and depends, in part, on first-pass effects. A xenobiotic must diffuse through a number of membranes before it can reach its site of action. These membranes are predominantly composed of phospholipids and cholesterol. Transport through membranes occurs via passive diffusion through the membrane, filtration (bulk flow is the major mechanism of transport that occurs with water directly through water pores [aquapores] for small molecules with a molecular weight [MW] <100), carrier-mediated active or facilitated transport, and, rarely, endocytosis. Most xenobiotics traverse membranes via simple passive diffusion. The driving force for passive diffusion is the difference in concentration of the xenobiotic on both sides of the membrane. Also, the larger the surface area, the higher the rate of diffusion. Most ingested xenobiotics are absorbed more rapidly in the small intestine than in the stomach because of the tremendous increase in surface area created by the presence of microvilli. To a substantial degree, the more lipid soluble an agent is, the more easily the agent crosses membranes. The extent of ionization also affects their rate of passive diffusion. Because nonpolar and noncharged molecules penetrate membranes better, weak acids cross membranes more rapidly in an acidic environment, and weak bases move more rapidly in a basic environment. Specialized transport mechanisms either require energy (adenosine triphosphate [ATP] dependent) to transport xenobiotics against a concentra-

tion gradient (active transport), or they can be energy independent (ATP independent) and lack the ability to transport against a concentration gradient (facilitated transport). *P-glycoprotein*, is an example of a transmembrane protein that is used for carrier-mediated, active (ATP-dependent) transport. P-glycoprotein is an efflux transporter located in the intestines, renal proximal tubule, hepatic bile canaliculi, and blood–brain barrier that is responsible for transporting compounds from inside to outside the cell. Filtration is generally considered to be of limited importance in the absorption of most xenobiotics, but is substantially more important with regard to elimination. Endocytosis, which describes the encircling of a xenobiotic by a cellular membrane, is responsible for the absorption of large macromolecules such as the oral Sabin polio vaccine.

Gastrointestinal absorption is affected by dosage form, degree of ionization, and partition coefficient, as well as by patient factors such as gastrointestinal blood flow, gastrointestinal motility, and the presence or absence of food, ethanol, or other interfering substances. The formulation is extremely important in predicting GI absorption. Disintegration and dissolution must precede absorption. Controlled-release, extended-release, and sustained-release formulations are designed to permit delivery of the xenobiotic over a prolonged period of time. Dissolution is affected by ionization, solubility, and the partition coefficient, as noted earlier. In the overdose setting, the formation of poorly soluble or adherent masses, such as concretions (meprobamate) and bezoars (bromide), significantly delays the time to onset of toxicity. Most ingested xenobiotics are primarily absorbed in the small intestine as a result of the large surface area and extensive blood flow of the small intestine.

Bioavailability, as mentioned earlier, is a measure of the amount of xenobiotic that reaches the systemic circulation unchanged. The fractional absorption (F) of a xenobiotic is defined by the area under the curve (AUC) of the designated route of absorption as compared to the AUC of the intravenous route. Gastric emptying and activated charcoal are used to decrease the bioavailability of ingested xenobiotics. Presystemic elimination may decrease or increase the bioavailability of a xenobiotic or a metabolite. The GI tract contains microbial organisms that can metabolize or degrade xenobiotics such as digoxin and oral contraceptives and enzymes such as peptidases that metabolize insulin. However, in rare cases, gastrointestinal hydrolysis can convert a xenobiotic into a toxic metabolite, as occurs when amygdalin is enzymatically hydrolyzed to produce cyanide. Xenobiotic-metabolizing enzymes and P-glycoprotein can also affect bioavailability. Xenobiotic-metabolizing enzymes (such as alcohol dehydrogenase) are found in the lumen of the small intestine and can substantially decrease the absorption of a xenobiotic. Venous drainage from the stomach and intestine delivers orally administered xenobiotics to the liver via the portal vein, thereby avoiding direct delivery to the systemic circulation. Subsequent hepatic metabolism occurs before the xenobiotic reaches the blood and is referred to as the *first-pass effect*.

DISTRIBUTION

After the xenobiotic reaches the systemic circulation, it is available for transport to peripheral tissue compartments. Both the rate and extent of distribution depend on many of the same principles that were discussed with regard to diffusion. Additional factors include affinity of the xenobiotic for plasma

and tissue proteins, acid–base status of the patient (which affects ionization), and physiologic barriers to distribution (blood–brain barrier, placental transfer, blood–testis barrier). Blood flow accounts for the initial phase of distribution, whereas xenobiotic affinities determine the final distribution pattern.

Plasma and serum concentrations are terms often used interchangeably by medical personnel. When a reference or calculation is made with regard to a concentration in the body, it is actually a plasma concentration. When concentrations are measured in the laboratory, a serum concentration (clotted and centrifuged blood) is often determined. In reality, serum and plasma are nearly equivalent.

Volume of distribution (Vd) is the proportionality term used to relate the dose of the xenobiotic the individual receives to the resultant plasma concentration. Vd is an apparent or theoretical volume into which a drug distributes. It is a measure of how much drug is located inside and outside of the plasma compartment, because only the plasma compartment is able to be routinely assayed. If 42 g of a xenobiotic is administered to a 70-kg man, and the total remained exclusively in the plasma compartment (Vd = 0.04 L/kg), the concentration is 15 g/L. If the distribution of the 42 g of xenobiotic approximated total body fluid (such as methanol) (0.6 L/kg), the concentration is 100 mg/dL. These calculations can be performed by using the following equation:

$$V_d = \frac{S \times F \times \text{dose (mg)}}{C_0}$$

Several plasma proteins bind xenobiotics and act as carriers and storage depots. The percentage of protein binding varies as a consequence of affinity and reversibility. Once bound to plasma protein, a xenobiotic with high binding affinity will remain largely confined to the plasma until elimination occurs. Most plasma measurements of xenobiotic concentration reflect total drug (bound plus unbound). Only the unbound drug is free to diffuse through membranes for distribution or for elimination. Albumin binds primarily to weakly acidic, poorly water-soluble xenobiotics, which include salicylates, phenytoin, and warfarin, as well as endogenous substances like free fatty acids, cortisone, aldosterone, thyroxine, and bilirubin. α_1-Acid glycoprotein usually binds basic xenobiotics, including lidocaine, imipramine, and propranolol. Although drug interactions are often attributed to the displacement of xenobiotics, usually concurrent metabolic interactions are more consequential. Saturation of plasma proteins following an overdose often leads to increased adverse effects. Saturation of plasma protein binding with salicylates and iron after overdose increases distribution to the CNS (salicylates) or to the liver, heart, and other tissues (iron), producing increased toxicity.

Specific therapeutic maneuvers in the overdose setting are designed to alter xenobiotic distribution by inactivating and/or enhancing elimination to limit toxicity. These therapeutic maneuvers include (a) manipulation of serum or urine pH (salicylates); (b) use of chelators (lead); and (c) the use of antibodies or antibody fragments (digoxin).

The Vd permits predictions about plasma concentrations and also assists in defining whether an extracorporeal method of removal is beneficial for a particular toxin. If the Vd is large (>1 L/kg), it is unlikely that hemodialysis, hemoperfusion, or exchange transfusion would be effective because most of the xenobiotic is outside of the plasma compartment.

ELIMINATION

Removal of a parent compound from the body (*elimination*) begins as soon as the xenobiotic is delivered to clearance organs such as the liver, kidneys, and lungs. Elimination begins immediately, but may not be the predominant kinetic process until absorption and distribution are substantially completed. As expected, the functional integrity of the major organ systems (cardiovascular, lungs, renal, hepatic) are major determinants of the efficiency of xenobiotic removal and of therapeutically administered antidotes.

Elimination can be accomplished by biotransformation to one or more metabolites, or by *excretion* from the body of unchanged xenobiotic. Excretion can occur via the kidneys, lungs, GI tract, and body secretions (sweat, tears, milk). Hydrophilic (polar) or charged xenobiotics and their metabolites, because of their water solubility, are generally excreted via the kidney. The majority of xenobiotic metabolism occurs in the liver, but it also commonly occurs in the blood, skin, GI tract, placenta, and kidneys. Lipophilic (noncharged or nonpolar) xenobiotics are usually metabolized in the liver to hydrophilic metabolites, which are then excreted by the kidneys.

Metabolic reactions, catalyzed by enzymes, categorized as either phase I or phase II, generally result in pharmacologically inactive metabolites; active metabolites may have different toxicities than the parent compounds. *Phase I,* or preparative metabolism, which may or may not precede phase II, is responsible for introducing polar groups onto nonpolar xenobiotics by oxidation, reduction, and hydrolysis or dealkylation. *Phase II,* or synthetic reactions, conjugate the polar group with glucuronide, sulfate or acetate, methyl groups, glutathione, and amino acids. The enzymes involved in these reactions have low substrate specificity, and those in the liver are usually localized to either the endoplasmic reticulum (microsomes) or the soluble fraction of the cytoplasm (cytosol). The enzymes that metabolize the largest variety of xenobiotics are heme-containing proteins referred to as *cytochrome P* (CYP) *450 monooxygenase enzymes* (formerly called the mixed function oxidase system). *Polymorphism* (individual genetic expression of isozymes), stereoisomer variability (enantiomers with different potencies and isozyme affinities), and the ability to metabolize a xenobiotic by alternate pathways contribute to unexpected metabolic outcomes.

Excretion is primarily accomplished by the kidneys, although, as mentioned earlier, biliary, pulmonary, and body fluid secretions contribute to lesser degrees. Urinary excretion occurs through glomerular filtration, tubular secretion, and passive tubular reabsorption. The glomerulus filters unbound xenobiotics of a particular size and shape in a manner that is not saturable, subject to renal blood flow and perfusion. Passive tubular reabsorption accounts for the reabsorption of noncharged, lipid-soluble xenobiotics, and is therefore influenced by the pH of the urine and the pK_a of the xenobiotic.

CLASSIC VERSUS PHYSIOLOGIC COMPARTMENT TOXICOKINETICS

Models exist to study and describe the movement of xenobiotics in the body with mathematical equations. The *one-compartment model* is the simplest for analytic purposes and is applied to xenobiotics that rapidly enter and distribute throughout the body. This model assumes that changes in plasma concentrations will result in and reflect proportional changes in tissue concentrations. Many xenobiotics, such as digoxin, lithium, and lidocaine, do not

instantaneously equilibrate with the tissues and are better described by a two-compartment model. In the *two-compartment model*, a xenobiotic is distributed instantaneously to highly perfused tissues (central compartment) and then is secondarily, and more slowly, distributed to a peripheral compartment. Elimination is assumed to take place from the central compartment.

If the rate of a reaction is directly proportional to the concentration of xenobiotic, it is termed *first order* or *linear*. Processes that are capacity limited or saturable are termed *nonlinear* (not proportional to the concentration of xenobiotic) and are described by the *Michaelis-Menten* equation, which is derived from enzyme kinetics. Graphing the ln (natural logarithm) of the concentration of the xenobiotic at various times for a first-order reaction is a straight line. The equation

$$C_t = C_0 e^{-kt}$$

describes the events when only one first-order process occurs. In this model, regardless of the concentration of the xenobiotic, the rate (percentage) of decline is constant. The time necessary for the xenobiotic concentration to be reduced by 50% is called the *half-life*. The half-life is determined by the equation

$$t_{1/2} = \frac{0.693}{k_e} \text{ where } k_e = \frac{\ln C_1 - \ln C_2}{t_1 - t_2}$$

The rate of reaction of a saturable process is not linear (not proportional to the concentration of xenobiotic) when saturation occurs. The rate becomes fixed at a constant maximal rate regardless of the exact concentration of the xenobiotic, termed a zero-order reaction (Fig. 9–1). It is inappropriate to perform half-life calculations on a xenobiotic displaying zero-order behavior because the metabolic rates are continuously changing.

CLEARANCE

Clearance (Cl) is the relationship between the rate of transfer or elimination of a xenobiotic from plasma to the plasma concentration of the xenobiotic and is expressed in units of volume per unit time (ie, mL/min).

$$Cl = \frac{\text{Rate of elimination}}{C}$$

Clearance for a particular eliminating organ or for extracorporeal elimination is calculated with the following equation:

$$Cl = Q \times \frac{(C_{in} - C_{out})}{C_{in}} = Q \times ER$$

Cl = clearance for the eliminating organ or extracorporeal device

Q = blood flow to the organ or device

ER = extraction ratio

C_{in} = xenobiotic concentration in fluid (blood or serum) entering the organ or device

C_{out} = xenobiotic concentration in fluid (blood or serum) leaving the organ or device

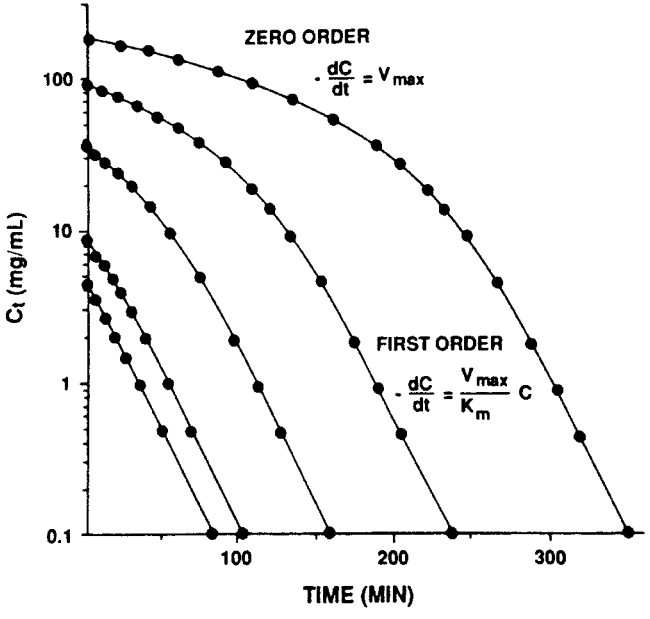


FIG. 9–1. Concentration versus time curve for a xenobiotic showing nonlinear pharmacokinetic concentrations where <10 mg/mL represent first order elimination. (*Reprinted, with permission, from Yang R, Andersen M: Pharmacokinetics. In: Hodgson E, Levi P, eds: Introduction to Biochemical Toxicology. Norwalk, CT, Appleton & Lange, 1994, p. 57.*)

For a first-order process (one-compartment model), clearance is given by this equation:

$$Cl = k_e Vd$$

STEADY STATE

When exposure to a xenobiotic occurs at a fixed rate, the plasma concentration of the xenobiotic gradually achieves a plateau level at a concentration at which the rate of absorption equals the rate of elimination; this is termed *steady state*. The time to achieve 95% of steady-state concentration for a first-order process is dependent on the half-life and usually necessitates five half-lives.

INTERPRETATION OF PLASMA CONCENTRATIONS

For plasma concentrations to have significance there must be an established relationship between effect and plasma concentration. For many medications (eg, phenytoin, digoxin, carbamazepine, and theophylline) there is an established therapeutic range. However, there are also many drugs for which there is no established therapeutic range (eg, diazepam, propranolol, verapamil). Some agents exhibit *hysteresis* in which the effect increases as the plasma concentration decreases (eg, physostigmine). For many xenobiotics, there is very little information on toxicodynamics. Often, sequential plasma concen-

trations are collected for retrospective analysis in an attempt to correlate plasma concentrations and toxicity. Tolerance to drugs such as ethanol also influences the interpretation of plasma concentrations.

Pitfalls in interpretation arise when the units for a particular plasma concentration are not obtained or are unfamiliar (eg, mmol/L) to the clinician. In the overdose setting, the type of analysis used is not generally applied to such large concentrations, and the laboratory may make errors in dilution, or errors can be inherent in the assay. Active metabolites may contribute to toxicity and may not be measured. Collection of accurate data for analysis requires at least four data points during one elimination half-life. During extracorporeal methods of elimination, ideal criteria for determining the amount removed require assay of the dialysate or charcoal cartridge or multiple simultaneous serum concentrations going into and out of the device, and not random serum concentrations.

When applied correctly, the concepts of pharmacokinetics, pharmacodynamics, toxicokinetics, and toxicodynamics can provide valuable information to help assess toxicity and judge response to therapy. Caution must be exercised, however, not to exceed the limitations of the analyses and always reassess the clinical status of the patient before making decisions based solely on calculations.

10 Principles and Techniques Applied to Enhance Elimination

Enhancement of the elimination of a xenobiotic from a poisoned patient is a logical step after techniques to inhibit absorption such as orogastric lavage, activated charcoal, or whole-bowel irrigation are initiated. In this chapter, hemodialysis, hemoperfusion, and hemofiltration are considered *extracorporeal therapies* because xenobiotic removal occurs in a blood circuit outside the body. All of these methods are used infrequently because current methods of intensive supportive care keep the overall mortality rate low in poisoned patients who reach the hospital alive. Because elimination techniques are not without adverse effects and complications, they are indicated in only a relatively small proportion of patients.

INDICATIONS FOR ENHANCED ELIMINATION

Enhanced elimination may be indicated in several types of patients:

- Patients who fail to respond adequately to full supportive care.
- Patients in whom the normal route of elimination of the xenobiotic is impaired.
- Patients in whom the amount of xenobiotic absorbed or its high concentration in serum indicates that serious morbidity or mortality is likely. Xenobiotics in this group include ethylene glycol, lithium, methanol, paraquat, salicylates, and theophylline.
- Patients with concurrent disease or in an age group (very young or old) associated with increased risk of morbidity or mortality from the overdose. Such patients are intolerant of prolonged coma, immobility, and hemodynamic instability.
- Patients with concomitant electrolyte disorders that could be addressed by hemodialysis. An example is the lactic acidosis associated with metformin toxicity.

CHARACTERISTICS OF XENOBIOTICS APPROPRIATE FOR EXTRACORPOREAL THERAPY

The appropriateness of any modality for increasing the elimination of a given xenobiotic depends on various properties of the molecules in question. Effective removal is limited by a large volume of distribution (Vd). A drug with a relatively small Vd, considered amenable to extracorporeal elimination, distributes in an apparent volume not much larger than total body water. Total body water is approximately 60% of total body weight, so that a Vd equal to total body water is approximately 0.6 L/kg body weight. Additionally, high protein binding may interfere with many of the techniques used to enhance elimination. Finally, when assessing the efficacy of any technique of enhanced elimination, a generally accepted principle is that the intervention is worthwhile only if the total body clearance of the xenobiotic is increased by at least 30%. This substantial increase is easier to achieve when the compound has a low endogenous clearance.

TECHNIQUES AVAILABLE TO ENHANCE REMOVAL OF XENOBIOTICS

Although controversies remain about the efficacy of, or need for, removal of many xenobiotics, a consensus regarding the indications for a number of procedures has developed. This consensus has led to consistent application of several techniques of elimination enhancement for some toxic exposures that occur relatively more frequently. The techniques to enhance xenobiotic elimination most commonly applied over the last decade have been alkalinization of the urine for salicylates; hemodialysis for methanol, ethylene glycol, lithium, and salicylates; and hemoperfusion or hemodialysis for theophylline.

Forced Diuresis and Manipulation of Urinary pH

Forced diuresis by volume expansion with isotonic sodium-containing solutions, such as 0.9% NaCl or lactated Ringer solution, may increase renal clearance of some molecules. The effect is potentially more important in patients who have had contraction of the extracellular fluid volume as a result of sodium loss. After the extracellular fluid volume is restored, continued infusion of saline increases urine volume proportionally more than the glomerular filtration rate (GFR), which may increase excretion of some small molecules such as urea, but which has marginal efficacy in the case of most poisonings where urine flow is not a significant determinant of excretion. The significant risk of this therapy is extracellular fluid volume overload, manifested by pulmonary and cerebral edema. Administration of diuretics such as furosemide along with saline may diminish the risk of extracellular fluid volume overload, but complicate the therapy, confuse the assessment of extracellular fluid volume, and increase the risk of metabolic alkalosis and hypokalemia. The unproven efficacy of forced diuresis in the management of *any* overdose has led most experts to abandon its use.

Many xenobiotics are weak acids or bases that are ionized in aqueous solution to an extent that depends on the pK_a of the compound and the pH of the solution. Knowing these variables, the Henderson-Hasselbalch equation can be used to determine the relative proportions of the acids, bases, and buffer pairs. Cell membranes are relatively impermeable to ionized, or polar molecules (such as an unprotonated salicylate anion), whereas nonionized, nonpolar forms (such as the protonated, noncharged salicylic acid) can cross more easily. As xenobiotics pass through the kidney, they may be filtered, secreted, and reabsorbed. If the urinary pH is manipulated to favor the formation of the ionized form in the tubular lumen, the drug is trapped in the tubular fluid and not passively reabsorbed into the bloodstream ("ion trapping"). Hence the rate and extent of its elimination can be increased. To make manipulation of urinary pH worthwhile, the renal excretion of the compound must be a major route of elimination.

Acidification of the urine by systemic administration of HCl or NH_4Cl to enhance elimination of weak bases, such as phencyclidine or amphetamines, is not useful and is potentially dangerous. The technique has been abandoned because it does not significantly enhance removal of xenobiotics and is complicated by systemic metabolic acidosis.

Alkalinization of the urine to enhance elimination of weak acids has a limited role for xenobiotics such as salicylates, phenobarbital, chlorpropamide, formate, diflunisal, fluoride, methotrexate, and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). These weak acids are ionized at alkaline urine pH and

tubular reabsorption is thereby greatly reduced. Alkalinization is achieved by the intravenous administration of sodium bicarbonate, 1–2 mEq/kg body weight every three to four hours. The goal is to increase urinary pH to 7–8.

The risk of extracellular fluid volume overload with sodium bicarbonate administration is the same as with the administration of 0.9% NaCl. Hypernatremia after administration of hypertonic sodium bicarbonate may also ensue. Bicarbonaturia is also associated with urinary potassium losses, so serum potassium concentration should be monitored frequently and KCl given liberally as long as the GFR is not impaired. A further complication of alkalemia is a decrease of ionized calcium, which becomes bound by albumin as protons are titrated off serum proteins; if this occurs, tetany may occur. Increasing urine pH by decreasing proximal tubular bicarbonate reabsorption via administration of carbonic anhydrase inhibitors such as acetazolamide is not recommended.

Peritoneal Dialysis

Although peritoneal dialysis is a relatively simple method to enhance xenobiotic elimination, it is too slow to be clinically useful. Peritoneal dialysis is, therefore, never the method of choice unless hemodialysis and hemoperfusion are unavailable and transfer to a center that can offer these techniques is not feasible. Besides exchange transfusion, it may be the only practical option in small children if experience with extracorporeal techniques in younger age groups is lacking, or until a child can be transported to an appropriate center.

Hemodialysis

The usefulness of hemodialysis for treatment of toxicity caused by lithium, toxic alcohols, salicylates, and theophylline is unquestionable. The technical details of the performance of hemodialysis for treatment of poisonings do not differ markedly from those used in the treatment of acute renal failure. Vascular access is best attained via the femoral vein. The subclavian and internal jugular veins are also acceptable, but have slightly higher complication rates, such as pneumothorax and arterial puncture. Hemodialysis and hemoperfusion are usually performed using a double-lumen catheter specially manufactured for dialysis. Blood is pumped from one lumen, passes through the machine, and is returned to the venous circulation through the second lumen. Blood flow rates with these catheters can be as high as 450–500 mL/min, although 350 mL/min is sometimes the maximum rate achieved. The blood lines and artificial kidney (the dialysis membrane) should be primed with an appropriate volume of fluid to reduce or avoid hypotension when the procedure is started. Larger “high-efficiency” or “high-flux” artificial kidneys should be selected. Full anticoagulation with heparin is usually required. A typical adult heparin dose is 4000–5000 units as a bolus, followed by 400–500 units hourly.

In poisoned patients, hemodialysis is usually performed for four to eight hours. During conventional hemodialysis, blood flows through hollow fibers that are semipermeable membranes. The hollow fibers are bathed by a dialysis solution, or dialysate. Xenobiotics diffuse across the membrane from blood into the dialysate down their concentration gradients. Table 10–1 lists the characteristics of xenobiotics that make them amenable to hemodialysis. In addition to removing xenobiotics, hemodialysis can correct acid–base and electrolyte abnormalities such as metabolic acidosis or alkalosis, hyperkale-

TABLE 10–1. Characteristics of Xenobiotics That Allow Clearance by Hemodialysis, Hemoperfusion, and Hemofiltration

For All Three Techniques
Low volume of distribution (<1 L/kg)
Single-compartment kinetics
Low endogenous clearance (<4 mL/min/kg)
For Hemodialysis
MW <500 daltons (<1000 daltons for high flux)
Water soluble
Not bound to plasma proteins
For Hemoperfusion
Adsorption by activated charcoal
Binding by plasma proteins does not preclude
For Hemofiltration
MW <10,000 or <40,000 daltons, depending on filter used

mia, and extracellular fluid volume overload. Hemodialysis is therefore preferred for poisonings characterized by these disorders, if clearance rates resulting from hemoperfusion and hemodialysis are relatively similar. Examples include salicylates, poisoning which is often associated with metabolic acidosis, and propylene glycol toxicity, which is often associated with lactic acidosis, especially in the presence of renal or hepatic impairment.

Complications of acute hemodialysis are relatively rare. Bleeding or thrombosis at the site used for vascular access, usually the femoral vein, is infrequent with normal hemostasis and adequate postprocedure tamponade of the catheter site. Bleeding in the gastrointestinal tract and elsewhere, caused by systemic anticoagulation with heparin, can be avoided if low doses of heparin are used. Low-dose heparin is an appropriate choice when dialyzing patients for toxic alcohol exposures who are at risk for intracerebral bleeding. Nosocomial bacteremia can occur if central lines are left in place for prolonged periods; central lines should be removed after five days at most. Femoral venous lines should always be removed in patients who are out of bed.

Charcoal Hemoperfusion

In general, if a xenobiotic is adsorbed by activated charcoal, charcoal hemoperfusion clearance will exceed that of hemodialysis. During hemoperfusion, blood is pumped through a cartridge containing a very large surface area of sorbent, either activated charcoal or carbon. The sorbent is coated with a very thin layer of polymer membrane which prevents direct contact between blood and sorbent, improves biocompatibility, and helps to prevent charcoal embolization. The adsorptive capacity of the cartridge is reduced with use because of deposition of cellular debris and blood proteins, and saturation of active sites by the xenobiotic in question. Estimation of residual adsorptive capacity by serial serum concentrations is usually not practical because of time delays in obtaining results. The cartridge should therefore be changed after two hours of use. As with hemodialysis, patients must be anticoagulated with heparin, and regional heparinization of the cartridge is possible if full anticoagulation is undesirable. Hemoperfusion is usually performed for 4–6 hours at flow rates of 250–400 mL/min.

The characteristics of xenobiotics that make them amenable to hemoperfusion (summarized in Table 10–1) differ from those for hemodialysis in the important respect that hemoperfusion is not limited by plasma protein binding.

Hemodialysis and hemoperfusion have been performed in series for procainamide, thallium, theophylline, and carbamazepine overdoses, with greater apparent clinical efficacy than with either procedure alone. In this technique, blood circulates first through the hemodialysis membrane, and then through the charcoal cartridge. If blood traverses the dialysis membrane first, some of the xenobiotic is dialyzed, and the activated charcoal cartridge has less drug to adsorb. The activated charcoal cartridge is exhausted more slowly, and higher extraction ratios are maintained.

The complications of hemoperfusion are similar to those of hemodialysis. In addition, patients often develop thrombocytopenia, leukopenia, and hypocalcemia. Better membrane encapsulation techniques have made embolization of charcoal particles extremely rare. As in the case of hemodialysis, doses of drugs used therapeutically may need to be increased if they are removed by hemoperfusion.

Continuous Hemofiltration and Hemodiafiltration

Continuous, as opposed to intermittent, modalities of dialytic therapy are still relatively unproven for the treatment of poisoning. These techniques find relatively common and widespread usage in the treatment of acute renal failure in the intensive care unit, and in this context are referred to collectively as modalities of *continuous renal replacement therapies* (CRRTs). The clearances of either urea or xenobiotics that are achieved with these techniques are significantly lower than those achieved with hemodialysis.

There are several possible advantages of continuous modalities. One is the capability to continue therapy for 24 hours each day. Therefore, hemofiltration can be instituted after hemodialysis or hemoperfusion to further remove a xenobiotic after it redistributes from tissue to blood. This is an attractive modality for slow, continuous removal of drugs such as lithium, which distributes slowly from tissue-binding sites or from the intracellular compartment.

Hemofiltration, or ultrafiltration, refers to the movement of plasma across a semipermeable membrane in response to hydrostatic pressure gradients. Table 10–1 summarizes the properties of xenobiotics that make them amenable to hemofiltration. However, the rate of removal with this form of therapy may be insufficient to benefit critically ill patients. The continuous modalities may be best suited for patients with hypotension who cannot tolerate conventional hemodialysis or hemoperfusion.

In pure hemofiltration, sometimes called *slow continuous ultrafiltration* (SCUF), there is no dialysate solution on the other side of the dialysis membrane. Small solutes, such as urea or sodium, are transported across the membrane with plasma water, a mechanism known as *convective transport* or *bulk flow*. Solute clearance can be significantly enhanced by adding a diffusive mechanism (dialysis), thus permitting a dialysate solution to bathe the blood-filled capillaries running countercurrent to the blood flow. The combination of hemofiltration with dialysis is known as *hemodiafiltration*. For all of these procedures, the patient must be fully anticoagulated, but some hemofilters are available that may not require anticoagulation. The hydrostatic pressure required for hemofiltration can be derived either from the patient or from a blood pump. In continuous arteriovenous hemofiltration (CAVH), blood is pumped through the filter by the patient's arterial pressure via a single-lumen femoral artery catheter returning to a femoral vein catheter. Continuous venovenous hemofiltration (CVVH) differs from CAVH because a blood pump is required

to maintain adequate flow rates, and arterial puncture with large-bore catheters is avoided. The addition of a dialysate bathing solution to the hemofiltration apparatus changes CAVH and CVVH to the augmented CAVHD (CAVH with dialysis) and CVVHD (CVVH with dialysis), respectively.

Plasmapheresis and Exchange Transfusion

Plasmapheresis and exchange transfusion are intended to eliminate xenobiotics with large molecular weights that are not dialyzable. This would include xenobiotics and endogenous molecules with molecular weights greater than 150,000 daltons, typified by immunoglobulins. By removing plasma proteins, both techniques offer the consequent potential benefit of removal of protein-bound molecules such as *Amanita* toxins, thyroxine, vincristine, and complexes of digoxin and antidigoxin antibodies. However, there is little evidence that either technique affects the clinical course and prognosis.

Pheresis is particularly expensive, and both pheresis and exchange transfusion expose the patient to the risks of infection with plasma- or blood-borne diseases. Replacement of the removed plasma during plasmapheresis can be accomplished with fresh-frozen plasma, albumin, or combinations of both. The former is associated with manifestations of hypersensitivity, such as fever, urticaria, wheezing, and hypotension, in as many as 21% of cases.

A different setting in which exchange transfusion may be an appropriate technique is in the management of small infants or neonates in whom dialysis or hemoperfusion may be technically difficult or impossible. Anticoagulation and multiple-dose activated charcoal (MDAC) may be hazardous and therefore contraindicated in the neonatal nursery where the risk of intracerebral bleeding and necrotizing enterocolitis is high. In premature neonates, a single volume exchange appears to alleviate manifestations of theophylline toxicity. The therapy has been successfully used to treat other pediatric poisonings, including severe salicylism.

Toxicology of Hemodialysis

Unlike patients who receive acute hemodialysis once or twice in the management of poisoning, patients with chronic renal failure are repeatedly exposed to large volumes of water derived from municipal reservoirs during the course of their hemodialysis treatments. If an "average" regimen consists of three four-hour treatments each week, with dialysate flows of 600 mL/min, patients will be exposed to more than 400 L of water separated from them only by a semipermeable membrane designed to allow solute passage in either direction. Consequently, problems with dialysate generation have the potential to be lethal to this population by exposing them to significant quantities of xenobiotics. Two potential sites of dialysate contamination exist: in the municipality's reservoirs and water treatment plants and in the dialysis unit.

Contamination of dialysate at the municipal water supply can occur as a result of runoff of chemicals into reservoirs or as a result of the municipality's addition of some chemical, inadvertently or intentionally. Chlorine and chloramine are frequently added to municipal water supplies to control bacterial populations. Chlorine can combine with nitrogenous compounds and form chloramine, which can cause nausea, vomiting, methemoglobinemia, and hemolytic anemia. Aluminum is present in some municipal water supplies, and before it was recognized as a problem, aluminum led to encephalopathy characterized

by seizures, myoclonus, and dementia, to osteomalacia, and to microcytic anemia.

Unusual microbes are also associated with serious toxicity. Untreated water at one center in Brazil demonstrated growth of Cyanobacteria (blue-green algae) and production of microcystins, cyclic peptides that cause serious hepatic toxicity; patients dialyzed with the contaminated water had a dramatic rate of death from liver failure.

11 Use of the Intensive Care Unit

Over the past several decades, use of the intensive care unit (ICU) and its attendant resources has led to improved survival from many serious conditions. This is the direct result of the ability to continuously monitor physiologic parameters, pay meticulous attention to supportive care, and use the most modern medical technology and treatment. Most critically ill, poisoned patients have acutely reversible conditions that will clearly benefit from intensive care intervention.

Unlike many patients with diseases managed in the ICU, poisoned patients often do not have a well-recognized clinical course or predictable complications. More than almost any other disease managed in the ICU, uncertainties typify toxicologic emergencies. A patient's history is often unreliable with regard to the kind of poison ingested, time of ingestion, and amount ingested. The poison may have unknown or unpredictable toxic effects. The therapies, antidotes, and complications of acute poisoning may be unfamiliar to the ICU staff. These uncertainties challenge healthcare providers and influence decisions about admitting patients to the ICU.

Often a patient will be admitted to the ICU, not for intervention, but for observation and monitoring. Intensive care units allow healthcare providers the best opportunity to minimize morbidity and decrease mortality. However, ICU care is very expensive and has contributed significantly to the escalation of healthcare costs.

The ICU admission guidelines presented in this chapter are intended to encourage effective use of ICU resources without compromising patient care. Current medical literature allows us to develop only very general guidelines. Future clinical studies addressing the use of healthcare resources for the poisoned patient will allow refinement of these guidelines. Although it is impossible to be all-inclusive, this chapter provides a decision-making strategy for most xenobiotics discussed in this text.

ARE THERE OTHER CRITERIA TO HELP SELECT THOSE POISONED PATIENTS NEEDING ICU ADMISSION?

Severity of Illness Models and ICU Admission

The Acute Physiology and Chronic Health Evaluation (APACHE II/III), the Mortality Probability Model (MPM II), and the Pediatric Risk of Mortality (PRISM II/III) are widely studied and generally accepted severity-of-illness models that score certain physiologic parameters and other factors in order to estimate risks and predict outcomes in critically ill individuals. Additional acute clinical assessment tools, such as the Simplified Acute Physiology Score (SAPS II) and the Glasgow Coma Score (GCS), are commonly used "bedside" methods of quickly assessing the severity of physiologic derangement and altered neurologic status, respectively. Clinical studies to validate such scoring systems included patients with a variety of medical and surgical conditions, although few trials have validated these scoring systems in large cohorts of poisoned patients.

Few studies have evaluated the use of the ICU for poisoned patients. Prospective studies have focused on mortality rates, use of resources, or types of xenobiotics ingested, whereas others, mostly retrospective, have focused on

patients exposed to a specific xenobiotic. More study is needed before any severity of illness model can be considered reliable in predicting which patients are at the highest risk of developing ICU-requiring morbidity or mortality.

Until more specific predictors of outcome are developed for individual xenobiotics, nothing is more useful than experience and good clinical judgment in predicting who may benefit from ICU admission. At present, withholding ICU care from poisoned patients based solely on a nonspecific "score" will not result in significant cost savings in the ICU, but may increase the risk of morbidity and mortality.

XENOBIOTIC-INDUCED END-ORGAN TOXICITY AS THE BASIS FOR ICU ADMISSION

The presence of certain signs, symptoms, or abnormal diagnostic tests requires ICU observation or intervention, regardless of the presumed xenobiotic exposure. This approach is most consistent with the philosophy of "treating the patient and not the poison," and may prove most helpful for patients with polydrug ingestions.

Examples of clinical conditions that likely require ICU care include the following:

- Vital signs: profound alteration in any vital sign, including temperature
- Central nervous system (CNS): delirium, coma, status epilepticus
- Respiratory: dyspnea, persistent hypoventilation, acute lung injury, hypoxia
- Cardiac: dysrhythmias, hypotension, hypertension, and tissue ischemia
- Gastrointestinal: hepatic failure
- Renal/metabolic: severe metabolic acidosis, electrolyte disturbances

Xenobiotic Characteristics as Basis for ICU Admission

In addition to end-organ toxicity, the xenobiotic, its treatment, and specific patient characteristics should influence ICU admission decisions. Well-described, expected toxic effects assist in early recognition of poisoning. ICU admission is generally warranted for patients expected to manifest serious clinical effects from a xenobiotic exposure. Examples include sustained-release medications and cardioactive drugs (eg, calcium channel blockers). Failure to appreciate the potential for serious, delayed toxic effects is a major pitfall in managing poisoned patients.

Patient Factors as Criteria for ICU Admission

Many elderly patients have chronic medical problems and do not tolerate major physiologic stressors without significant compromise. Conditions that alter drug metabolism or elimination, such as renal or hepatic disease, may prolong toxicity or produce toxicity after lesser amounts are ingested.

Physiologic Monitoring and Specialized Treatment as Requirements for ICU Admission

The ICU setting offers highly skilled staff and modern technology to manage complex medical problems. It also provides a nurse-to-patient ratio that allows for frequent or continuous monitoring of basic physiologic parameters. Invasive monitoring, including intraarterial monitoring and pulmonary artery catheters, is valuable for managing the patient with hypotension, intravascular volume depletion, or respiratory failure from acute lung injury (ALI).

Most critically ill, poisoned patients have acute, reversible conditions requiring supportive care measures (eg, ventilator support, vasopressor support, and close monitoring) that ICUs are best equipped to provide. Most often, supportive care measures improve the outcome of critically ill, poisoned patients more than antidotes and specialized treatments. Focus on supportive care measures, such as maintaining a patent airway, preventing hypoxia with the administration of oxygen, and treatment of shock, decreased the mortality for patients with barbiturate overdoses from 20% in the 1930s to less than 2% in the 1950s. Both adult and pediatric studies report good outcomes in most critically ill, overdosed patients treated with only mechanical ventilation, vasopressor support, and careful monitoring.

ALTERNATIVES TO ICU ADMISSION

Often, placing patients in the ICU solely for observation is an ineffective use of this expensive resource. When information about the xenobiotic, the patient, and the capabilities of the medical unit are all considered, many patients can be safely observed outside the ICU. Alternatives to the ICU include a medical or pediatric floor bed, an intermediate care unit, a telemetry-monitored bed, a medical psychiatric unit, or an emergency department observation unit. Capabilities for managing poisoned patients may vary considerably between institutions and in different types of patient care areas. Table 11–1 identifies some considerations to assist with disposition decisions.

TABLE 11–1. Considerations for Intensive Care Unit Admission

Xenobiotic characteristics
Are there known serious sequelae (eg, cyclic antidepressant cardiotoxicity)?
Can the patient deteriorate rapidly from its toxic effects?
Is the onset of toxicity likely to be delayed (eg, sustained-release preparation, slowed GI motility, or delayed toxic effects)?
Does the xenobiotic have cardiac effects that will require cardiac monitoring?
Is the amount ingested a potentially serious or potentially lethal dose?
Is the required or planned therapy unconventional (eg, large doses of atropine for treating overdoses of organic phosphorus insecticides)?
Does the therapy have potentially serious adverse effects?
Is there insufficient literature to describe the potential human toxic effects?
Are potentially serious coingestants likely (must take into account the reliability of the history)?
Patient characteristics
Does the patient have any signs of serious end-organ toxicity?
Is there progression of the end-organ effects?
Are laboratory data suggestive of serious toxicity?
Are drug concentrations rising?
Is the patient at high risk for complications requiring ICU intervention?
Seizures
Unresponsive to verbal stimuli
Level of consciousness impaired to the point of potential airway compromise
PCO_2 >45 mm Hg
Systolic blood pressure <80 mm Hg
Cardiac dysrhythmias
Prolonged ECG complexes and intervals (QRS duration ≥0.10 sec; QT prolongation)

(continued)

TABLE 11–1. Considerations for Intensive Care Unit Admission *(Continued)*

- Does the patient have preexisting medical conditions that could predispose to complications?
  - Chronic alcohol or drug dependence
  - Chronic liver disease
  - Chronic renal failure or insufficiency
  - Heart disease
  - Pregnancy
- Is the patient suicidal?

Assessing the capabilities of the inpatient unit/observation unit

- Does the admitting team (attending, house staff, students) appreciate the potential seriousness of a toxicologic emergency?
- Is the nursing staff:
  - Familiar with this toxicologic emergency?
  - Familiar with the potential for serious complications?
- Is the staffing adequate to monitor the patient?
  - What is the ratio of nurses to patients?
  - Are time-consuming nursing activities required (eg, hourly urine pH assessments or whole-bowel irrigation)?
- Can a safe environment be provided for a suicidal patient?
  - Can a patient have suicide precautions and monitoring with a medical floor bed?
  - Can a one-to-one observer be present in the room with the patient?
  - Can the patient be restrained?

Many poisoned patients use ICU resources because they are suicide risks. Other than the ICU, many hospitals cannot provide an alternative for observing a high-risk, suicidal patient. Less costly alternatives are available, but they must assure a safe environment for suicidal patients. An emergency department observation unit, an intermediate care unit, a medical psychiatric unit, or a one-on-one observer can safely observe these patients.

PART B THE FUNDAMENTAL PRINCIPLES OF MEDICAL TOXICOLOGY

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Section I. Biochemical and Molecular Basis

12 Chemical Principles

Chemistry is the science of matter; as such, it encompasses the structure, physical properties, and reactivities of atoms and their compounds. In many respects, toxicology is the science of the interactions of matter with physiologic entities. As such, chemistry and toxicology are intimately linked. The study of the principles of inorganic, organic, and biochemistry offers important insight into the mechanisms and clinical manifestations of xenobiotics and poisoning, respectively. This chapter reviews many of these tenets and provides relevance to the current practice of medical toxicology.

THE STRUCTURE OF MATTER

Basic Structure

Matter includes the substances of which everything is made. *Elements* are the foundation of matter, and all matter is made from one or more of the known elements. An *atom* is the smallest quantity of a given element that retains the properties of that element. Atoms consist of a nucleus, incorporating protons and neutrons, coupled with its orbiting electrons. The *atomic number* is the number of protons in the nucleus of an atom, and is a whole number that is unique for each element. Although the vast majority of carbon nuclei have 6 neutrons in addition to the protons, accounting for an *atomic mass* (ie, protons plus neutrons) of 12 (^{12}C), a small proportion of naturally occurring carbon nuclei, called *isotopes*, have 8 neutrons and an atomic mass of 14 (^{14}C). This is why the *atomic weight* of carbon displayed on the periodic table is 12.011, and not 12, as it actually represents the average atomic masses of all isotopes found in nature weighted by their frequency of occurrence. Moreover, ^{14}C is actually a *radioisotope*, which is an isotope with an unstable nucleus that emits radiation (particles and/or rays), presumably in an effort to attain a stable state (Chap. 128). The atomic weight, measured in grams/mole (g/mol), also indicates the molar mass of the element. That is, in 1 atomic weight (12.011 g for carbon) there is 1 mole of atoms (6.023×10^{23} atoms).

Elements combine chemically to form *compounds*, which generally have physical and chemical properties that differ from those of the constituent elements. The elements in a compound can only be separated by chemical means that destroy the original compound (eg, burning). This differentiates compounds from *mixtures*, which are combinations of elements or compounds that can be separated by physical means (eg, distillation).

INORGANIC CHEMISTRY

The Periodic Table

Dimitri Mendeleev, a Russian chemist in the mid-19th century, recognized that when all of the known elements were arranged in order of atomic weight, certain patterns of reactivity became apparent. The result of his work was the Periodic Table of the Elements (Fig. 12–1), which, with some minor alterations, is still an essential tool today. Broadly, the periodic table is divided into metals and nonmetals. Metals, in their pure form, are typically malleable solids that conduct electricity, whereas nonmetals are usually dull, fragile, nonconductive compounds (C, N, P, O, S, Se, halogens). The metals are found on the left side of the periodic table and account for the majority of the elements, whereas the nonmetals are on the right side. Separating the two groups are the metalloids, which fall on a jagged line starting with boron (B, Si, Ge, As, Sb, Te, At). The metalloids have chemical properties that are intermediate between the metals and the nonmetals. Because the chemistry of the elements varies dramatically based on the chemical form (ie, organic, inorganic, or elemental), as well as the ionic charge, prediction of the clinical effects of a particular element is often difficult.

The Alkali (Group IA: Li, Na, K, Rb, Cs, Fr) and Alkaline Earth (Group IIA: Be, Mg, Ca, Sr, Ba, Ra) Metals

Alkali metals and hydrogen (not an alkali metal on Earth) have a single outer valence electron and lose this electron easily to form compounds with a valence of 1+. The alkaline earth metals (between the alkali and rare earth, group IIIB) readily lose 2 electrons, and their cations have a 2+ charge. In their metallic form, members of both of these groups react violently with water to liberate strongly basic solutions, accounting for their group names ($2Na^0 + 2H_2O \rightarrow 2NaOH + H_2$).

The Transition Metals (Groups IB to VIIIB)

Unlike the alkali and alkaline earth metals, most other metallic elements are neither soluble nor reactive. This includes the transition metals, a large group that contains several ubiquitous metals such as iron (Fe) and copper (Cu). The ionic forms, unlike the metallic form, of these elements are typically highly reactive and toxicologically important. Because the transition metals have partially filled valence shells, they are capable of obtaining several, usually positive, oxidation states. This important mechanism explains the role of transition metals in oxidation-reduction (redox) reactions, generally as electron acceptors (see Oxidation–Reduction below). This reactivity is used by living organisms in various physiological catalytic and coordination roles, such as at the active sites of enzymes and in hemoglobin, respectively. Expectedly, the substantial reactivity of these transition metal elements is highly associated with cellular injury caused by the generation of reactive oxygen species.

The Heavy Metals

Heavy metal is often loosely used to describe all metals of toxicologic significance, but in reality, the term should be reserved to describe only those metals in the lower period of the periodic table, particularly those with atomic masses greater than 200. The chemical properties and toxicologic predilection of this group vary among the elements, but their unifying toxicologic

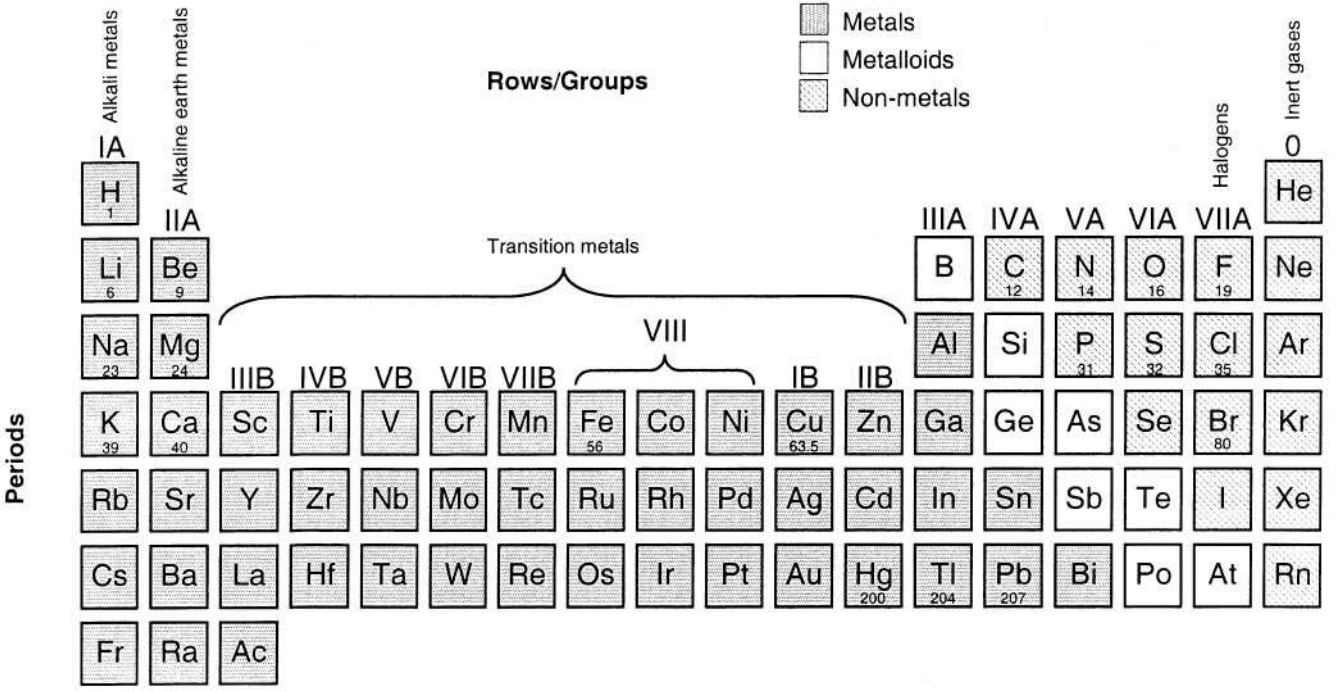

FIG. 12–1. The periodic table of the elements. *(continued)*

Symbol	Name	Atomic Number	Atomic Weight
Ac	Actinium	89	227.0278
Al	Aluminum	13	26.9815
Am	Americium	95	243.06
Sb	Antimony	51	121.75
Ar	Argon	18	39.948
As	Arsenic	33	74.9216
At	Astatine	85	209.99
Ba	Barium	56	137.33
Bk	Berkelium	97	247.07
Be	Beryllium	4	9.0122
Bi	Bismuth	83	208.9804
Bh	Bohrium	107	262
B	Boron	5	10.81
Br	Bromine	35	79.904
Cd	Cadmium	48	112.41
Ca	Calcium	20	40.08
Cf	Californium	98	251.08
C	Carbon	6	12.011
Ce	Cerium	58	140.12
Cs	Cesium	55	132.9054
Cl	Chlorine	17	35.453
Cr	Chromium	24	51.996
Co	Cobalt	27	58.9332
Cu	Copper	29	63.546
Cm	Curium	96	247.07
Db	Dubnium	105	262
Dy	Dysprosium	66	162.5
Es	Einsteinium	99	252.08
Er	Erbium	68	167.26
Eu	Europium	63	151.96
Fm	Fermium	100	257.1
F	Fluorine	9	18.9984
Fr	Francium	87	223.02
Gd	Gadolinium	64	157.25
Ga	Gallium	31	69.72
Ge	Germanium	32	72.59
Au	Gold	79	196.9665
Hf	Hafnium	72	178.49
Hs	Hassium	108	265
He	Helium	2	4.0026
Ho	Holmium	67	164.9304
H	Hydrogen	1	1.0079
In	Indium	49	114.82
I	Iodine	53	126.9045
Ir	Iridium	77	192.22
Fe	Iron	26	55.847
Kr	Krypton	36	83.8
La	Lanthanum	57	138.9055
Lr	Lawrencium	103	260.11
Pb	Lead	82	207.2
Li	Lithium	3	6.941
Lu	Lutetium	71	174.97
Mg	Magnesium	12	24.305
Mn	Manganese	25	54.938
Mt	Meitnerium	109	266
Md	Mendelevium	101	258.1
Hg	Mercury	80	200.59
Mo	Molybdenum	42	95.94
Nd	Neodymium	60	144.24
Ne	Neon	10	20.179
Np	Neptunium	93	237.0482
Ni	Nickel	28	58.7
Nb	Niobium	41	92.9064
N	Nitrogen	7	14.0067
No	Nobelium	102	259.1
Os	Osmium	76	190.2
O	Oxygen	8	15.9994
Pd	Palladium	46	106.4
P	Phosphorus	15	30.9738
Pt	Platinum	78	195.09
Pu	Plutonium	94	244.06
Po	Polonium	84	208.98
K	Potassium	19	39.0983
Pr	Praseodymium	59	140.9077

FIG. 12–1. *(Continued).*

Symbol	Name	Atomic Number	Atomic Weight
Pm	Promethium	61	146.92
Pa	Protactinium	91	231.0359
Ra	Radium	88	226.0254
Rn	Radon	86	222.02
Re	Rhenium	75	186.207
Rh	Rhodium	45	102.9055
Rb	Rubidium	37	85.4678
Ru	Ruthenium	44	101.07
Rf	Rutherfordium	104	261
Sm	Samarium	62	150.4
Sc	Scandium	21	44.9559
Sg	Seaborgium	106	263
Se	Selenium	34	78.96
Si	Silicon	14	28.0855
Ag	Silver	47	107.868
Na	Sodium	11	22.98977
Sr	Strontium	38	87.62
S	Sulfur	16	32.06
Ta	Tantalum	73	180.9479
Tc	Technetium	43	98.906
Te	Tellurium	52	127.6
Tb	Terbium	65	158.9254
Tl	Thallium	81	204.37
Th	Thorium	90	232.0381
Tm	Thulium	69	168.9342
Sn	Tin	50	118.69
Ti	Titanium	22	47.9
W	Tungsten	74	183.85
U	Uranium	92	238.029
V	Vanadium	23	50.9414
Xe	Xenon	54	131.3
Yb	Ytterbium	70	173.04
Y	Yttrium	39	88.9059
Zn	Zinc	30	65.38
Zr	Zirconium	40	91.22

FIG. 12–1. *(Continued).*

mechanism is electrophilic interference with nucleophilic sulfhydryl-containing enzymes.

The Metalloids (B, Si, Ge, As, Sb, Te, At)

Although the metalloids share many physical properties with the metals, they are differentiated because of their propensity to form compounds with both metals and the nonmetals carbon, nitrogen, and oxygen. Thus, metalloids may be either oxidized or reduced in chemical reactions.

The Nonmetals (C, N, P, O, S, Se, Halogens)

The nonmetals are highly electronegative and, unlike the metals, may be toxic in either their compounded or their elemental form. The nonmetals with

high electronegativity, such as O_2 or Cl_2, generally oxidize other elements in chemical reactions. Those with lower electronegativity, such as C, behave as reducing agents.

The Halogens (F, Cl, Br, I, At) In their highly reactive elemental form, which contains a covalent dimer of halogen atoms, the halogens carry the suffix -ine (eg, Cl_2, chlorine). Halogens are strong oxidizing agents. Because they are highly electronegative, they form halides (eg, Cl^-, chloride) by abstracting electrons from less electronegative elements. Thus the halogen ions, in their stable ionic form, generally carry a charge of –1. The halides, although much less reactive than their respective elemental forms, are reducing agents. The hydrogen halides (eg, HCl, hydrogen chloride) are gases under standard conditions, but they ionize when dissolved in aqueous solution to form the hydrohalidic acids (eg, HCl, hydrochloric acid). All hydrogen halides except HF ionize completely in water to release H^+ and are considered *strong acids*. Because of its small ionic radius, lack of charge dispersion, and intense electronegativity, hydrogen fluoride ionizes poorly and is a *weak acid*. This specific property of HF has important toxicologic implications (Chap. 101).

Group 0: The Inert Gases (He, Ne, Ar, Kr, Xe, Rn)

Inert gases, also known as noble gases, maintain completed valence shells and are thus entirely unreactive except under extreme experimental conditions. However, despite their lack of chemical reactivity, the inert gases are toxicologically important as simple asphyxiants. Radon is radioactive, and prolonged exposure is associated with the development of lung cancer.

Bonds

Electrons are not generally shared evenly between atoms when they form a compound. The degree to which an element draws the shared electron is determined by the element's *electronegativity* (Fig. 12–2). Several types of bonds exist between elements when they form compounds. When one element gains valence electrons and another loses them, the resulting elements are charged and attract one another in an *ionic*, or *electrovalent*, bond (eg, NaCl, or table salt).

IA							0
H 2.20	IIA		IIIA	IVA	VA	VIA	VIIA	He –
Li 0.98	Be 1.57		B 2.04	C 2.55	N 3.04	O 3.44	F 3.98	Ne –
Na 0.93	Mg 1.31		Al 1.61	Si 1.90	P 2.19	S 2.58	Cl 3.16	Ar –
K 0.82	Ca 1.00				As 3.18	Se 2.55	Br 2.96	Kr –

FIG. 12–2. Electronegativity of the common elements. Note that the inert gases are not reactive and thus do not have electronegativity.

Compounds formed by two elements of similar electronegativity have little ionic character because there is little impetus for separation of charge. Instead, these elements share pairs of valence electrons, a process known as *covalence*. The resultant molecule contains a *covalent bond*, which is typically very strong and generally requires a high-energy chemical reaction to disrupt it. Rarely is sharing truly symmetric, as it is in oxygen (O_2) or chlorine (Cl_2). If sharing is asymmetric and the electrons thus exist to a greater degree around one of the component atoms, the bond is *polar*. However, the presence of a polar bond does not mean that the compound is polar.

Oxidation–Reduction

Redox reactions involve the movement of electrons from one atom or molecule to another, and actually comprise two dependent reactions: reduction and oxidation. *Reduction* is the gain of electrons by an atom that is thereby *reduced*. The electrons derive from a *reducing agent*, which in the process becomes *oxidized*. *Oxidation* is the loss of electrons from an agent, which is, accordingly, *oxidized*. An *oxidizing agent* accepts electrons, and in the process, is reduced. By definition, these chemical reactions involve a change in the valence of an atom.

Reactive Oxygen Species

Free radicals are reactive molecules that contain one or more unpaired electrons, and are typically neutral but may be anionic or cationic. However, because certain toxicologically important reactive molecules do not contain unpaired electrons, such as hydrogen peroxide (H_2O_2) and ozone (O_3), the term *reactive species* is preferred.

Reactive species are continually generated as a consequence of endogenous metabolism and there is an efficient system for their control. Under conditions of either excessive endogenous generation or exposure to exogenous reactive species, the physiologic defense against these toxic products is overwhelmed. When this occurs, reactive species induce direct cellular damage, as well as initiate a cascade of oxidative reactions that perpetuate the toxic damage.

The most important reactive oxygen species in medical toxicology are derived from oxygen, although those derived from nitrogen are also important. Table 12–1 lists some of the important reactive oxygen and nitrogen species.

Superoxide is generated within neutrophil and macrophage lysosomes as part of the oxidative burst, a method of eliminating infectious agents and damaged cells. Superoxide may subsequently be enzymatically converted, or dismutated, into hydrogen peroxide by superoxide dismutase (SOD). Hydrogen peroxide may be subsequently converted into hypochlorous acid by the enzymatic addition of chloride by myeloperoxidase.

Although superoxide and hydrogen peroxide are reactive oxygen species, it is their conversion into the hydroxyl radical (OH•) that accounts for their most consequential effects. The hydroxyl radical is generated by the Fenton reaction (Fig. 12–3), in which hydrogen peroxide is decomposed in the presence of a transition metal. This catalysis typically involves Fe^{2+}, Cu^{+}, Cd^{2+}, Cr^{5+}, Ni^{2+}, or Mn^{2+}. The Haber-Weiss reaction (Fig. 12–3), in which a transition metal catalyzes the combination of superoxide and hydrogen peroxide, is the other important means of generating the hydroxyl radical.

The most consequential toxicologic effects of reactive oxygen species occur on the cell membrane, and are caused by the initiation by hydroxyl radi-

TABLE 12–1. Structure of Important Reactive Oxygen and Nitrogen Species

	Structure
Reactive Oxygen Species	
Free radicals	
Hydroxyl radical	OH·
Alcoxyl radical	RO·
Singlet oxygen (Σ)	[O] or $^1O_2$
Peroxyl radical	ROO·
Superoxide radical	O_2^{-} or O_2^{-}
Nonradicals	
Hydrogen peroxide	H_2O_2
Hypochlorous acid	HOCl
Singlet oxygen (Δ)	[O] or $^1O_2$
Ozone	O_3
Reactive Nitrogen Species	
Free radicals	
Nitric oxide	NO·
Nitrogen dioxide	NO_2·
Nonradicals	
Peroxynitrite anion	$ONOO^-$
Nitronium cation	NO_2^+

cal of the lipid peroxidative cascade. The alteration of these lipid membranes ultimately causes membrane destruction. Identification of released oxidative products such as malondialdehyde is a common method of assessing lipid peroxidation.

Detoxification of certain reactive species is difficult because of their extreme reactivity. Widespread antioxidant systems exist to trap reactive species before they can damage tissues. An example is the availability of glutathione, a reducing agent and nucleophile, to prevent both exogenous oxidants from producing hemolysis and the acetaminophen metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI) from damaging the hepatocyte.

Acid–Base Chemistry

Even in neutral solution, a tiny proportion of water is always undergoing ionization to form both H^+ and OH in exactly equal amounts. It is, however, the

$$H_2O_2 \xrightarrow[\text{TM}]{} OH^- + OH\bullet$$

Fenton

$$H_2O_2 + O_2^{\bullet-} \xrightarrow[\text{TM}]{} O_2 + OH^- + OH\bullet$$

Haber-Weiss

FIG. 12–3. The Fenton and Haber-Weiss reactions, which are the two most important mechanisms to generate hydroxyl radicals, are both mediated by transition metals (TM). Iron (Fe^{2+}) and copper (Cu^+) are typical transition metals.

quantity of H^+ that is of concern, and this is the basis of using the pH to characterize a solution. The number of H^+ ions increases when an acid is added to the solution and falls when an alkali is added. In an attempt to make this quantity more practical, the negative log of the H^+ concentration is calculated, which defines the *pH*. Thus, the negative log of 10^{-7} is 7, and the pH of a neutral aqueous solution is 7. In actuality, the pH of water is approximately 6 because of dissolution of ambient carbon dioxide to form carbonic acid ($H_2O + CO_2 \rightarrow H_2CO_3$), which ionizes to form H^+ and bicarbonate (HCO_3^-).

Because most of the acids or bases of toxicologic interest have ionizable protons or available electrons, respectively, the Brønsted-Lowry definition is most often considered when discussing acid–base chemistry (ie, $HA + H_2O \rightarrow H_3O^+ + A^-$; $B^- + H_2O \rightarrow HB + OH^-$). An acid is a substance that donates a proton, and a base is one that accepts a proton. However, this is not a defining property of all acids or bases, and other definitions exist.

Strong acids ionize completely in aqueous solution and very little of the parent compound remains. Weak acids, on the other hand, obtain an equilibrium between parent and ionized forms, and thus do not alter the pH to the same degree as a similar quantity of a strong acid. This chemical notation defines the strength or weakness of an acid and should not be confused with the concentration of the acid.

The degree of ionization of a weak acid is determined by the pK_a, or the negative log of the *ionization constant*, which represents the pH at which an acid is half dissociated in solution. The same relationship applies to the pK_b of an alkali, although by convention the pK_b is expressed as the pK_a ($pK_a = 14 - pK_b$). The lower the pK_a, the stronger the acid; the converse is true for bases. Because only uncharged compounds cross lipid membranes spontaneously, the pK_a has clinical relevance (eg, salicylic acid, pK_a of 3).

ORGANIC CHEMISTRY

The study of carbon-based chemistry and the interaction of inorganic molecules with carbon-containing compounds is called *organic chemistry*, because the chemistry of living organisms is carbon based. *Biochemistry* (Chap. 13) is a subdivision of organic chemistry; it is the study of organic chemistry within biologic systems.

Chemical Properties of Carbon

Carbon, atomic number 6, has a molecular weight of 12.011 g/mol. With few exceptions (notably cyanide ion and carbon monoxide), carbon forms 4 bonds in stable organic molecules. In organic compounds, carbon is commonly bonded to other carbon atoms, as well as to hydrogen, oxygen, nitrogen, and halide (ie, fluorine, bromine, or iodine) atoms. Under certain circumstances, carbon can be bonded to metals, as is the case with methylmercury.

Nomenclature

The most rigorous method to name organic compounds is in accordance with standards adopted by the International Union of Pure and Applied Chemistry (IUPAC; www.iupac.org); these names are infrequently used, especially for larger molecules, and *alternative chemical names* (based on the structure of a molecule) are common.

Bonding in Organic Chemistry

The vast majority of bonding in organic molecules is *covalent*, in which electrons are shared between 2 atoms.

Nucleophiles and Electrophiles

Many organic reactions of toxicologic importance can be described as the reactions of *nucleophiles* with *electrophiles*. *Nucleophiles* (literally, nucleus-loving) are species with increased electron density, frequently in the form of a lone pair of electrons (as in the cases of cyanide ion and carbon monoxide). Nucleophiles, by virtue of this increased electron density, have an affinity for atoms or molecules that are electron deficient; such moieties are called *electrophiles* (literally, electron-loving). The reaction of a nucleophile with an electrophile involves the movement of electrons, by forming and/or breaking bonds.

NAPQI is a toxicologically important electrophile (Fig. 12–4). NAPQI is formed when the endogenous detoxification pathways of acetaminophen metabolism (glucuronidation and sulfation) are overwhelmed (Chap. 34). As a result of the electron configuration of NAPQI, the carbon atoms adjacent to the *carbonyl carbon* (a carbonyl carbon is one that is double-bonded to an oxygen) are very electrophilic; the sulfur groups of cysteine residues of hepatocyte proteins react with NAPQI to form a characteristic *adduct*, 3-(cystein-*S*-yl)acetaminophen in a multistep process (an adduct is formed when one compound is added to another). Figure 12–4 diagrams the mechanism of the protein–NAPQI reaction (Chap. 34).

Although imprecise, the designations "hard" and "soft" help to predict, on a qualitative level, how nucleophiles and electrophiles interact with one another. "Hard" species have a charge (or partial charge) that is highly localized; that is, their charge-to-radius ratio is high. Fluoride, a small atom that cannot spread its electron density over a large area, is an example. Similarly, hard electrophiles are species in which the positive charge cannot be spread over a large area; ionized calcium, a small ion, is a hard electrophile.

"Soft" nucleophiles and electrophiles, on the other hand, are capable of delocalizing their charge over a larger area. In this case, the charge-to-mass ratio is low, either because the atom is large or because the charge can be spread over a number of atoms within a given molecule. Sulfur is the prototypical example of a soft nucleophile and the lead ion, Pb^{2+}, is a typical soft electrophile.

The usefulness of this classification lies in the observation that hard nucleophiles tend to react with hard electrophiles, and soft nucleophiles with soft electrophiles. For example, one of the principal toxicities of fluoride ion poisoning (Chap. 101) is hypocalcemia; this is because the fluoride ions (hard nucleophiles) readily react with calcium ions (hard electrophiles). Conversely, the soft nucleophile lead is effectively chelated by soft electrophiles such as the sulfur atoms in the chelators dimercaprol (see Antidotes in Brief: Dimercaprol [British Anti-Lewisite or BAL]) and succimer (see Antidotes in Brief: Succimer [2,3-Dimercaptosuccinic Acid]).

Functional Groups

There is perhaps no concept in organic chemistry as powerful as that of the *functional group*. Functional groups are atoms or groups of atoms that confer

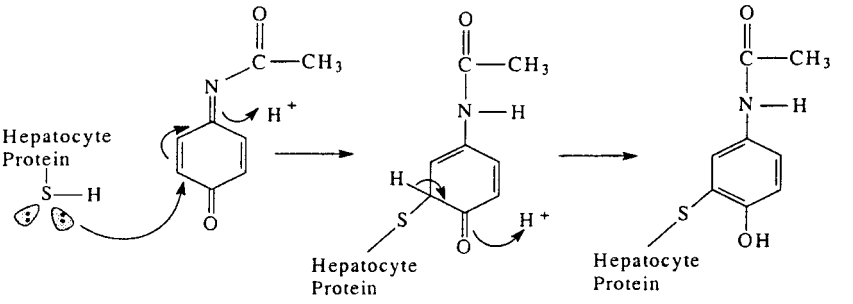

FIG. 12–4. The reaction of cysteine residues on hepatocyte proteins with NAPQI to form the characteristic adducts 3-(cystein-*S*-yl) APAP.

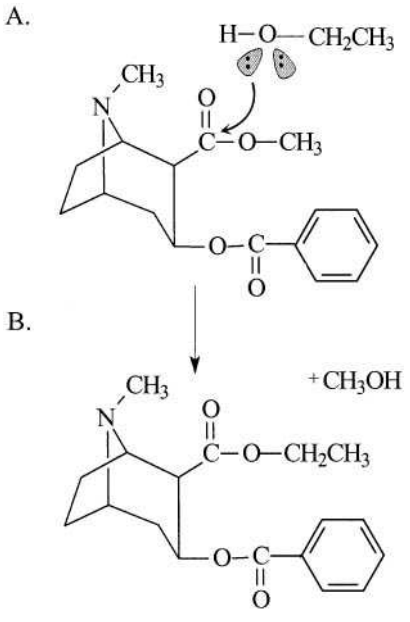

FIG. 12–5. Reaction of cocaine with ethanol **(A)** to form cocaethylene and methanol **(B).**

similar reactivity on a molecule; of less importance is the molecule to which it is attached. Some representative functional groups in organic chemistry and toxicology are the *hydrocarbons* (*alkanes* and *alkenes*), *alcohols*, *carboxylic acids*, and *thiols.* Molecules with a given functional group often have more in common with molecules within the same functional group than they have in common with the molecules from which they were derived.

Hydrocarbons, as their name implies, consist of only carbon and hydrogen. *Alkanes* are hydrocarbons that contain no multiple bonds. *Alkenes* contain carbon-carbon double bonds. *Alkynes*, which contain carbon-carbon triple bonds, are of limited toxicologic importance.

Alcohols possess the hydroxyl (OH) functional group, which adds polarity to the molecule and makes alcohols highly soluble in other polar substances, such as water. In biologic systems, alcohols are generally CNS depressants, but they can also act as nucleophiles. For example, ethanol may react with cocaine to form cocaethylene (Fig. 12–5; see Chap. 74 for clinical details).

Carboxylic acids contain the functional group COOH. As their name implies, they are acidic, and the pK_a of carboxylic acids is generally 4 or 5, depending on the substitution of the molecule. Carboxylic acids are capable of producing a significant anion gap metabolic acidosis, which is true whether the acids are endogenous or exogenous. Examples of endogenous acids are β-hydroxybutyric acid and lactic acid; examples of exogenous acids are formic acid (produced by the metabolism of methanol) and glycolic, glyoxylic, and oxalic acids (produced by the metabolism of ethylene glycol).

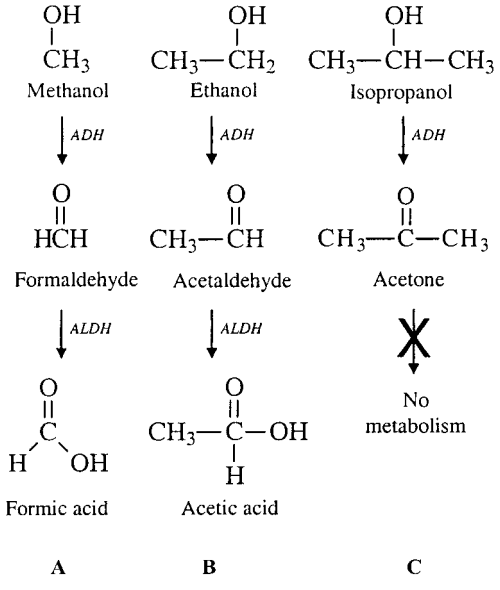

FIG. 12–6. Oxidative metabolism of **(A)** methanol, **(B)** ethanol, and **(C)** isopropanol. Note that acetone does not undergo further oxidation in vivo. ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase.

Thiols contain a sulfur atom, which usually functions as a nucleophile. The sulfur atom of *N*-acetylcysteine can regenerate glutathione reductase, and can also react directly with NAPQI to detoxify this electrophile. The sulfur atoms of many chelators, such as dimercaprol and succimer, are nucleophiles that are very effective at chelating electrophiles such as heavy metals.

In addition to conferring different physical properties on the molecule, the addition of the alcohol functional group also confers different chemical properties and reactivities. For example, methane, ethane, and propane are virtually incapable of undergoing oxidation in biologic systems. The alcohols formed by the addition of one or more hydroxyl groups, however, are readily oxidized by alcohol dehydrogenase (Fig. 12–6).

13 Biochemical and Metabolic Principles

Xenobiotics are compounds that are foreign to a living system. Xenobiotic toxins injure living organisms by interfering with critical metabolic processes, by causing structural damage to cells, or by altering the cellular genetic material. The specific biochemical sites of actions that disrupt metabolic processes are well characterized for many xenobiotics, although mechanisms of cellular injury are not.

The capacity of a xenobiotic to produce injury in a living organism is affected by many factors, including its absorption, distribution, elimination, site of activation or detoxification, site of action, and ability to cross membranes to access a particular organ. Sites of action include the active sites of enzymes or receptor binding sites, DNA, and lipid membranes. The route of exposure to a toxin may confine damage primarily to one organ: for example, pulmonary injury that follows inhalation; GI injury that follows a caustic ingestion; or injury to the skin following dermal exposure. Additionally, the ability to penetrate a certain organ may be related to factors such as the pK of the xenobiotic (eg, hydrofluoric acid, salicylates) or the availability of specific uptake mechanisms (eg, α-amanitin, paraquat).

GENERAL ENZYME CONCEPTS

The ability to detoxify and eliminate both endogenous toxins and exogenous xenobiotics is crucial to the maintenance of physiologic homeostasis and normal metabolic functions for all organisms. A simple example is the detoxification of cyanide, a potent cellular poison that is ubiquitous in the environment and is also a product of normal metabolism. Mammals have evolved the enzyme rhodanese, which combines cyanide with thiosulfate to create the less toxic, renally excreted compound thiocyanate.

Enzymes that act on more lipophilic xenobiotics, including the CYP (formerly cytochrome P450) enzymes, are embedded in the lipid membranes of the hepatic endoplasmic reticulum. Other enzymes are located in the liquid matrix of cells (cytosol).

BIOTRANSFORMATION OVERVIEW

The term *biotransformation* refers to the alteration of a xenobiotic as a result of enzyme action. The term *metabolism*, although sometimes used interchangeably with *biotransformation*, describes the entire process of absorption, biotransformation, and elimination of the xenobiotic.

Biotransformation usually results in "detoxification," a reduction in the toxicity of a substance and its removal from the body. In some cases, however, the metabolites produced may be more toxic than the parent xenobiotic ("toxification" or "metabolic activation"). A single xenobiotic may be a substrate for biotransformation by several metabolic pathways, some resulting in detoxification and others in metabolic activation.

The likelihood that a xenobiotic will undergo biotransformation depends on its chemical nature. Ionized compounds, such as carboxylic acids, are less likely to cross a lipid membrane to enter the body. When they do, the kidneys rapidly eliminate them. Very volatile compounds, such as dichloromethane,

are expelled promptly via the lungs. Neither of these groups of xenobiotics undergo significant enzymatic metabolism. Nonpolar, lipophilic xenobiotics that are less soluble in aqueous fluids require biotransformation to more water-soluble compounds before they can be excreted.

Most biotransformation reactions have two sequential phases. Phase I reactions add functional groups to lipophilic xenobiotics, converting them into more chemically reactive metabolites. This is usually followed by phase II reactions that conjugate the reactive products of phase I with other molecules that render them more water soluble, detoxifying the xenobiotic and facilitating its elimination. Some xenobiotics undergo only a phase I or a phase II reaction.

Oxidation Overview

Much of the activity that occurs during biotransformation or within critical metabolic pathways results in the oxidation or reduction of carbon. Oxidation involves the transfer of electrons from a substrate molecule to an electron-seeking (electrophilic) molecule, leading to reduction of the electrophilic molecule and oxidation of the substrate. These oxidation-reduction reactions are often coupled to the cyclical oxidation and reduction of a cofactor, such as the pyridine nucleotides, $NADPH/NADP^+$ (nicotinamide adenine dinucleotide phosphate) or $NADH/NAD^+$ (nicotinamide adenine dinucleotide). These nucleotides alternate between their reduced (NADPH, NADH) and oxidized ($NADP^+$, $NADH^+$) forms.

Electrons resulting from the catabolism of energy sources are extracted by NAD^+, forming NADH. NADH transports the electrons into the mitochondria where they enter the cytochrome-mediated electron transport system. This results in the production of adenosine triphosphate (ATP), the reduction of molecular oxygen, and the regeneration of NAD^+, a process that is critical to the maintenance of oxidative metabolism.

Phase I Biotransformation Reactions and the CYP Family

Phase I reactions are predominantly oxidation reactions that add functional groups suitable for conjugation during phase II. These include hydroxyl (OH), sulfhydryl (SH), amino (NH_2), aldehyde (COH), or carboxyl (COOH) moieties. The most numerous and important of the enzymes involved in phase I oxidation reactions are the CYP enzymes. Nearly 90% of oxidative transformation of xenobiotics is accomplished by 6 CYP enzymes: 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 (Table 13–1). The approximate amounts of liver CYP enzymes are 3A4 (40–55%), 2D6 (30%), 2C9 and 2C19 (10–20%), 2E1 (7%), and 1A2 (2%).

The substrate selectivity of some CYP enzymes is determined by molecular, electrical, and physicochemical properties of the substrates. The CYP1A subfamily has greater specificity for planar polyaromatic substrates such as benzo[*a*]pyrene. The CYP2E subfamily targets low-molecular-weight hydrophilic xenobiotics, whereas CYP3A4 has increased affinity for lipophilic compounds. Substrates of CYP2C9 are usually weakly acidic, whereas those of CYP2D6 are more basic. High specificity can also result from key structural considerations such as stereoselectivity. Some xenobiotics are racemic mixtures of stereoisomers. These may be substrates for different CYP enzymes and have distinct affinities for the enzymes, resulting in different rates of metabolism. For example, R-warfarin is biotransformed by CYP3A4 and CYP1A2, whereas S-warfarin is metabolized by CYP2C9.

TABLE 13–1. Characteristics of Different CYP Isozymes

Isozyme	1A2	2C9	2C19	2D6	2E1	3A4
Percent of liver CYPs	2%	10–20%		30%	7%	40–55%
Contribution to enterocyte CYPs	Minor	Minor	Minor	Minor	Minor	70%
Percent of metabolism of typically used drugs	2–15%	10%		25–30%		50–60%
Organs other than liver with isozyme	Lung, intestine, stomach	Nasal mucosa, stomach, heart, intestine	Nasal mucosa, heart, intestine	Lung, heart, intestine	Lung, intestine	Nasal mucosa, lung, stomach, intestine
Polymorphism[a]	No	Yes	Yes	Yes	No	No
Poor metabolizer						
African American		1–2%	20%	2–8%		
Asian		1–2%	15–20%	<1%		
White		1–3%	3–5%	5–10%		
Ultrarapid metabolizer						
Asian				1%		
Ethiopian				30%		
Northern Europeans				1–2%		
Southern Europeans				10%		

[a]Enzyme variations can exist even in those listed as “No” for polymorphism.

Genetic polymorphism of a biotransformation enzyme may result in an alteration of the activity rate of that enzyme. The genetic polymorphism of human populations results in very significant differences in the abilities of individuals to biotransform specific xenobiotics. Differences in biotransformation capacity that lead to toxicity, once thought to be "idiosyncratic," are likely a result of these inherited, unmeasured differences in the genetic complement of the individual. Three major metabolizer phenotypes are recognized: normal (extensive), poor (slow), and ultrarapid. The CYP2C19 and CYP2D6 genes are highly polymorphic (Table 13–1).

Besides being substrates, xenobiotics may induce or inhibit the activity of different CYP enzymes. A xenobiotic may inhibit or induce the activity of an enzyme even though it is not a substrate at that CYP site. For example, quinidine is biotransformed by CYP3A4, but it is a potent inhibitor of CYP2D6.

Heterogeneity of CYP enzymes results in differences in metabolic activity between individual patients. A prodrug may not be metabolized to its active form because the patient is a poor metabolizer or is taking a xenobiotic that inhibits the respective CYP enzyme. Conversely, a drug may not reach a therapeutic level because the patient is an ultrarapid metabolizer or is taking a second drug that induces the respective CYP enzyme.

Induction and Inhibition of CYP Enzymes

Enzyme induction is usually caused by increased expression of CYP genes, resulting in a net increase of enzyme protein synthesis. Induction of an enzyme results in more rapid biotransformation of a xenobiotic that is affected by the same enzyme. Because the clinical manifestations of enzyme induction rely on protein synthesis, there is a time delay in the onset and offset relative to starting and stopping the inducing xenobiotic.

Similar pharmacokinetic considerations affect the clinical manifestations of enzyme inhibition. Competitive inhibition, because of binding of the parent compound or a metabolite at substrate sites, usually begins within hours. A relatively rare mechanism of inhibition is the irreversible inhibition of a CYP enzyme by the reactive metabolite of a second xenobiotic at its substrate binding site. This so-called suicide inhibition results in the destruction of the bound CYP enzyme. Biotransformation by the affected CYP enzyme does not resume until new enzyme is produced.

Drug–drug interactions that involve CYP enzymes may be either pharmacodynamic or pharmacokinetic in nature. Pharmacodynamic interactions occur when the mechanism of action of one xenobiotic enhances or diminishes the effect produced by a second xenobiotic. Pharmacokinetic interactions occur when the effect of one xenobiotic alters the absorption, distribution, metabolism, and/or elimination of another, leading to a change in the effective concentration of the second xenobiotic at its site of action.

Specific CYP Enzymes

CYP1A2

This enzyme is involved in the metabolism of 15% of all pharmaceuticals used today. The CYP1 family is induced by polycyclic aromatic hydrocarbons found in cigarette smoke and charred food. This family bioactivates several procarcinogens including benzo[*a*]pyrene. Xenobiotics activated by CYP1 enzyme in the gastrointestinal tract are linked to colon cancer.

CYP3A4

CYP3A4 is the most abundant CYP in the human liver, comprising anywhere from 40–55% of the mass of hepatic CYP enzymes. The CYP3A4 enzyme is the most common one found in the intestinal mucosa and is responsible for much of the first-pass drug metabolism.

More than 120 xenobiotics are metabolized by CYP3A4. It is involved in the biotransformation of 50–60% of all pharmaceuticals. Substrates include dihydropyridine calcium channel blockers, cyclosporine, cisapride, many opioids, and many β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. An excellent historical example of an adverse drug interaction related to this enzyme is the QTc-interval prolongation and spontaneous ventricular tachycardia that occurred in patients taking terfenadine or astemizole in combination with ketoconazole or erythromycin. Ketoconazole inhibits CYP3A4, causing a 15–72-fold increase in serum levels of terfenadine. Bioflavonoids in grapefruit juice decrease metabolism of some substrates by 5–12-fold. The CYP3A4 enzyme does not exhibit genetic polymorphism; however, there are large interindividual variations in enzyme levels.

CYP2D6

Approximately one-third of human CYP enzymes are in the CYP2 enzyme family, which with 76 alleles, exhibits the greatest degree of genetic polymorphism. Twenty-five percent of all drugs used today, including 50% of the commonly used antipsychotics, are substrates for CYP2D6. It is sometimes called debrisoquine hydrolase as it was first identified while studying the metabolism of the antihypertensive agent debrisoquine.

Approximately 8% of whites and 5% of African Americans are poor metabolizers of CYP2D6 substrates. Perhexiline, an antianginal drug marketed in Europe in the 1980s, caused severe liver disease and peripheral neuropathy in persons with a demonstrated inability to metabolize debrisoquine. Decreased activity of CYP2D6 was implicated in the development of severe lactic acidosis in some patients taking phenformin.

CYP2E1

This enzyme comprises 7% of the total CYP enzyme content in the human liver. Although not considered to demonstrate genetic polymorphism, genetic changes account for a 2-fold increase in nasopharyngeal cancer in Chinese persons who smoke. Besides CYP1A2, this is the only other CYP enzyme linked to cancer. CYP2E1 is induced by a number of xenobiotics, including ethanol, phenobarbital, isoniazid, phenytoin, and cigarette smoke. The induction of CYP2E1 is associated with increased liver injury by reactive metabolites of carbon tetrachloride and of bromobenzene (Chap. 26). During the metabolism of substrates that include carbon tetrachloride, ethanol, acetaminophen, paranitrophenol, aniline, and *N*-nitrosomethylamine, CYP2E1 actively produces free radicals and other reactive metabolites associated with adduct formation and lipid peroxidation (Chap. 26). CYP2E1 is inhibited by acute elevations of ethanol, an effect illustrated by the capacity of acute administration of ethanol to inhibit the metabolism of methadone, resulting in higher brain concentrations. Acute ethanol ingestion also inhibits the metabolism of acetaminophen. The chronic ingestion of ethanol hastens its own metabolism through enzyme induction.

CYP2C9

The CYP2C9 enzyme is the most abundant isozyme of the CYP2C enzyme family, which comprises approximately 15% of the CYP enzymes in the liver. This enzyme is associated with polymorphism; poor metabolism occurs in 1–3% of whites and in 2% of Asians and African Americans. This enzyme biotransforms S-warfarin, the most active isomer of warfarin. There is an association between poor metabolism and an increased risk of bleeding in patients on warfarin.

Phase II Biotransformation Reactions

Phase II biotransformation reactions are synthetic reactions that catalyze rapid conjugation of the products of phase I reactions with endogenous molecules such as glucuronic acid, glutathione, sulfate, or some amino acids such as glycine, glutamic acid, and taurine. This conjugation terminates the pharmacologic activity of the xenobiotic and greatly increases its water solubility and excretability. Most phase II reactions occur in the cytosol and are faster than phase I reactions.

MECHANISMS OF CELLULAR INJURY

Synthesis of Toxins or "Mistaken" Toxins

Sometimes a xenobiotic is mistaken for a natural substrate by synthetic enzymes, which act on the xenobiotic and facilitate its injurious effect. The incorporation of the rodenticide fluoroacetate into the tricarboxylic acid cycle is an example of this mechanism of toxic injury (Fig. 13–1).

Injury by Metabolites at Distant Sites

Toxic metabolites may be synthesized at one site and transported to other target sites where they cause injury. Cyanide formed by the hepatic metabolism of acetonitrile nail removers produces toxicity at distant sites.

Injury by Metabolites of Biotransformation

Highly reactive metabolites exert damage at the site where they are synthesized. Tissue injury by reactive metabolites occurs commonly in the liver, the major site of biotransformation of xenobiotics. Similar injury may occur in other organs that have the capacity to biotransform xenobiotics to metabolites that result in local injury; these include the lungs, skin, kidneys, gastrointestinal tract, and even the nasal mucosa. Overdoses of acetaminophen lead to excessive hepatic production of the highly reactive electrophile *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which initiates a damaging covalent bond with hepatocytes (Chap. 34). Acute renal tubular necrosis also occurs in patients with an overdose of acetaminophen. This is attributed to its biotransformation by prostaglandin H synthase within renal tubular cells to a highly reactive semiquinoneimine.

Free Radical Formation

Free radicals are compounds that have an unpaired electron and are very reactive with other species because they seek to obtain another electron. They include the superoxide anion ($O_2\bar{\bullet}$), the hydroxyl radical (HO•), and hydrogen

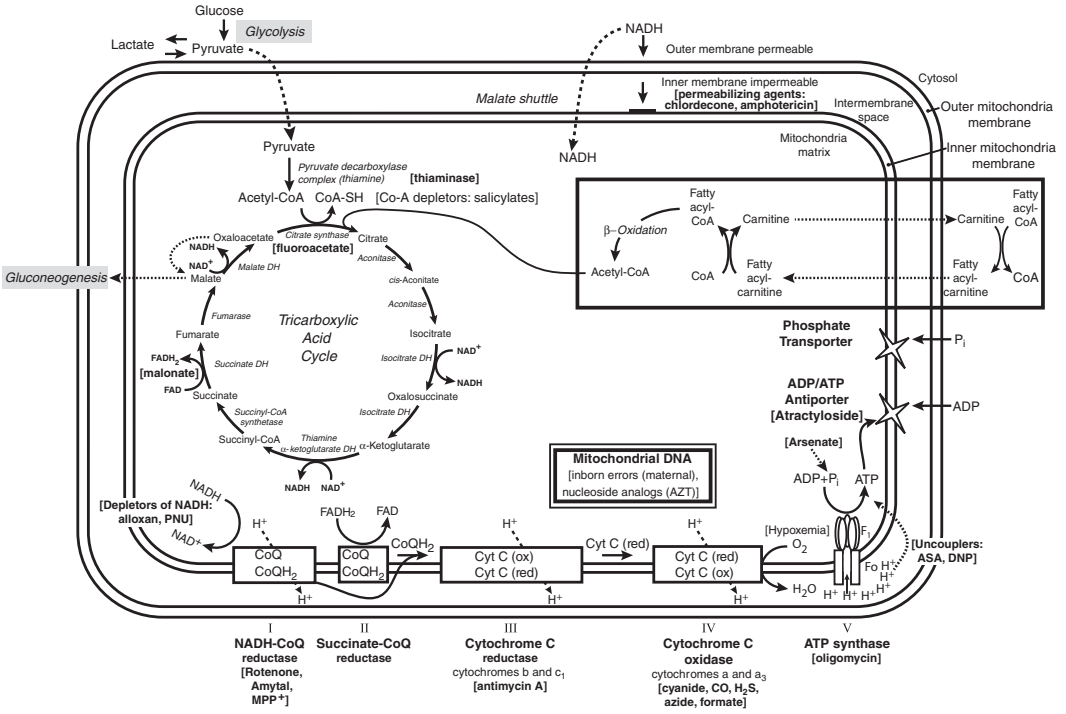

FIG. 13–1. Pyruvate is converted to acetylcoenzyme A (acetyl-CoA), which enters the Krebs cycle as shown. Reducing equivalents, in the form of NADH and flavin adenine dinucleotide (FADH), donate electrons to a chain of cytochromes beginning with NADH dehydrogenase. These reactions "couple" the energy released during electron transport to the production of adenosine triphosphate (ATP). Ultimately, electrons combine with oxygen to form water. The sites of toxins that inhibit oxidative metabolism are shown. The sites where thiamine functions as a coenzyme are also illustrated. DH = dehydrogenase.

peroxide (H_2O_2), among others. Free radicals are most destructive when they initiate chain reactions, such as when a free radical attacks polyunsaturated fatty acids in cellular membranes, resulting in lipid peroxidation. This attack removes a hydrogen atom from a methylene carbon and leaves an unpaired electron, causing the formation of a lipid radical. This lipid free radical attacks other unsaturated fatty acid chains, causing a chain reaction that destroys the cellular membrane. Membrane degradation products initiate inflammatory reactions in the cells, resulting in further damage.

Transition metals frequently catalyze the creation of oxygen free radicals. The following is an example of hydroxyl radical formation: (A) A first step is the addition of an electron to O_2 to create the superoxide ion. (B) The very reactive superoxide combines with hydrogen and another electron to produce hydrogen peroxide. (C) In the presence of a metal ion catalyst such as iron, hydrogen peroxide undergoes various reactions to produce the hydroxyl radical. The dot in these formulas represents an unpaired electron, the hallmark of a free radical.

(A) $O_2 + e^- \rightarrow O_2^{\bullet-}$

(B) $O_2^{\bullet-} + 2H^+ + e^- \rightarrow H_2O_2$

(C) $H_2O_2 + Fe^{2+} + O_2^{\bullet-} \rightarrow Fe^{3+} + O2 + OH^- + HO\bullet$ (Haber-Weiss reaction)

$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+}\ OH^- + HO\bullet$ (Fenton reaction)

CRITICAL BIOCHEMICAL PATHWAYS AND TOXINS THAT AFFECT THEM

High-energy phosphate bonds, predominantly in the form of adenosine triphosphate (ATP), fuel all energy-dependent cellular processes, such as synthesis, active transport, and maintenance of electrolyte balance and membrane integrity. When the production or use of ATP is inhibited, rapid cell dysfunction and death occurs. The ultimate goal of many metabolic processes is the production and mobilization of cellular energy. Numerous pathways interconnect glycogen, fat, and protein reserves in many tissues that store and retrieve ATP and glucose. The brain and red blood cells are entirely dependent on glucose for energy production, whereas other tissues can also use ketone bodies and fatty acids to synthesize ATP.

14 Neurotransmitters and Neuromodulators

Although many poisonous substances produce their primary toxic effects by affecting neurotransmission, xenobiotics rarely possess single pharmacologic actions. Given this complexity it is not always clear which neurotransmitter system is producing an observed effect at a particular time. Consequently, xenobiotics discussed in this chapter may be found in several sections.

NEURON PHYSIOLOGY AND NEUROTRANSMISSION

Membrane Potentials, Ion Channels, and Nerve Conduction

More than 40 different ion channels are described in various nerve terminals. Human beings have hundreds of different varieties of ion channels for Na^+, Cl^-, Ca^{2+}, and K^+, most of which fall into two general classes: voltage-gated (voltage-dependent) ion channels and ligand-gated ion channels. Voltage-gated channels open or close in response to changes in membrane potential. Ligand-gated channels open or close when a ligand (eg, neurotransmitter) binds to the channel.

Depolarization of a segment of the neurolemma causes the adjacent neuronal membrane to reach threshold, resulting in the propagation of an action potential. Sodium channel activation is quickly followed by inactivation. Over the short term, repolarization of the neuron mainly results from efflux of K^+ and some influx of Cl^-.

Neurotransmitter Release

Neurotransmitters are released from nerve endings into the synapse, where they produce effects by binding to receptors on postsynaptic and/or presynaptic cell membranes. The receptors may be on other neurons or effector organs such as smooth muscle.

Vesicle Transport of Neurotransmitters

Vesicular uptake pumps move neurotransmitters or their precursors from the cytoplasm into the vesicle lumen. The pH inside neurotransmitter vesicles is lower than that in the cytoplasm. Neurotransmitters are confined within the vesicle, to a great extent, by ion trapping, as they are more ionized in the relatively acid vesicle. Anything that decreases the pH gradient across the vesicle membrane results in the movement of neurotransmitters into the cytoplasm. For example, amphetamines move into vesicles, where they buffer protons, causing the movement of monoamine neurotransmitters out of vesicles.

Neurotransmitter Uptake

Most neurotransmitters have their synaptic effects terminated by active uptake into neurons and/or glial cells. These plasma membrane neurotransmitter transporters are distinct from those transporters responsible for movement of neurotransmitters into vesicles, are capable of moving neurotransmitters in either direction, and are not always completely specific for a particular substance.

Neuronal Excitation and Inhibition

Excitatory neurotransmitters usually act postsynaptically by causing Na^+ or Ca^{2+} influx, or by preventing K^+ efflux, triggering depolarization and an ac-

tion potential. Postsynaptic inhibition is usually accomplished by movement of Cl^- into the neuron or by movement of K^+ out of the neuron. Both processes hyperpolarize the neuron and move membrane potential farther away from threshold, making it more difficult to depolarize the membrane to threshold voltage.

When presynaptic inhibition (the prevention of neurotransmitter release) is mediated by the neurotransmitter released from the same neuron, the receptor is termed an *autoreceptor*. Stimulation of receptors on presynaptic nerve endings may also enhance, rather than inhibit, neurotransmitter release.

ACETYLCHOLINE

Acetylcholine (ACh) is a neurotransmitter of the central and peripheral nervous system. Centrally, it is found in both brain and spinal cord; cholinergic fibers project diffusely to the cerebral cortex. Peripherally, ACh serves as a neurotransmitter in autonomic and somatic motor fibers (Fig. 14–1).

Synthesis, Release, and Inactivation

Acetylcholine is synthesized from acetylcoenzyme A and choline. Acetylcholine undergoes degradation in the synapse to choline and acetic acid by acetylcholinesterase. Pseudocholinesterase (plasma cholinesterase) plays no role in the degradation of synaptic ACh metabolism. However, it does metabolize some drugs, including cocaine and succinylcholine.

Acetylcholine Receptors

After release from cholinergic nerve endings, ACh activates two main types of receptors: nicotinic and muscarinic (Fig. 14–1).

Nicotinic Receptors

Nicotinic receptors (nAChRs) reside in the CNS (mainly in spinal cord), on postganglionic autonomic neurons (both sympathetic and parasympathetic), and at skeletal neuromuscular junctions, where they mediate muscle contraction.

Muscarinic Receptors

Muscarinic receptors reside in the CNS (mainly in the brain), on end organs innervated by postganglionic parasympathetic nerve endings, and at most postganglionic sympathetically innervated sweat glands (Fig. 14–2).

Chemical Agents

Table 14–1 provides examples of common xenobiotics that affect cholinergic neurotransmission.

BIOGENIC AMINES

Norepinephrine and Epinephrine

Norepinephrine (NE), epinephrine (EPI), dopamine (DA), and serotonin (5-hydroxytryptamine; 5-HT) are referred to as biogenic amines, and their neurotransmitter systems are similar in many respects. Neurotransmitter synthesis, vesicle transport and storage, uptake, and degradation share many enzymes and structurally similar transport proteins. Norepinephrine is released from postganglionic sympathetic fibers (Fig. 14–3) and is also found in the CNS. The ad-

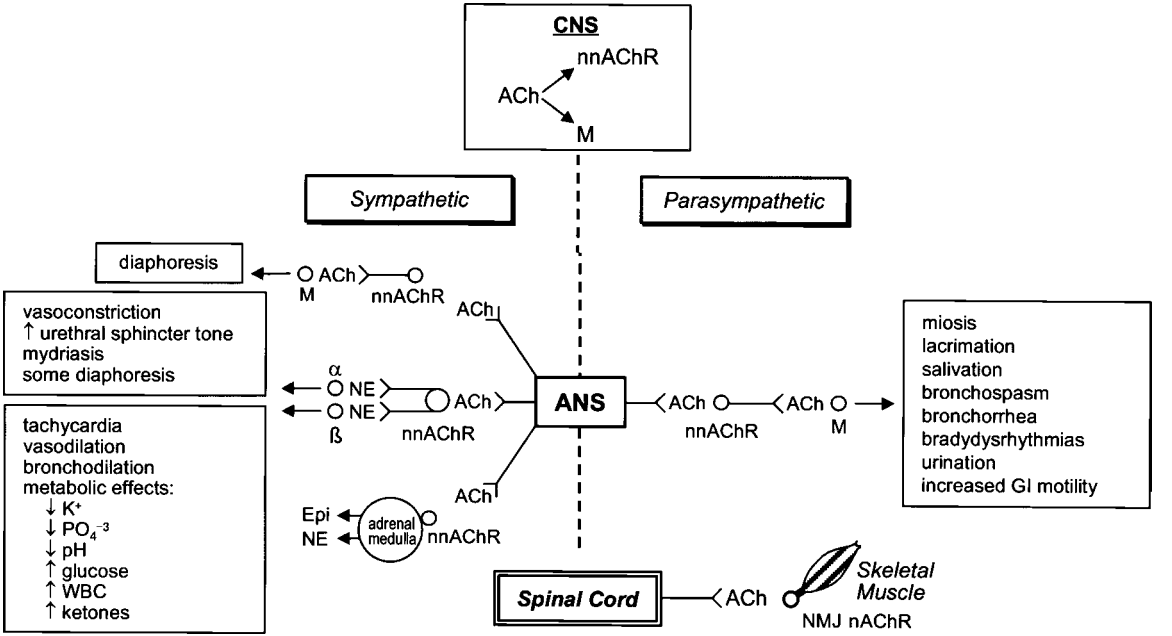

FIG. 14–1. Diagram of the cholinergic nervous system, including adrenergic involvement in the autonomic nervous system. ACh binds to CNS, ganglionic, and adrenal neuronal nicotinic receptors (nnAChRs) and to neuromuscular junction nicotinic receptors (NMJ nAChRs). ACh also binds to various subtypes of muscarinic (M) receptors in the CNS and on effector organs innervated by postsynaptic parasympathetic neurons and to most sweat glands. NE and/or EPI released in response to ganglionic ACh stimulation of nnAChRs activates α- and β-adrenoreceptors. ACh = acetylcholine; ANS = autonomic nervous system; CNS = central nervous system; EPI = epinephrine; NE = norepinephrine.

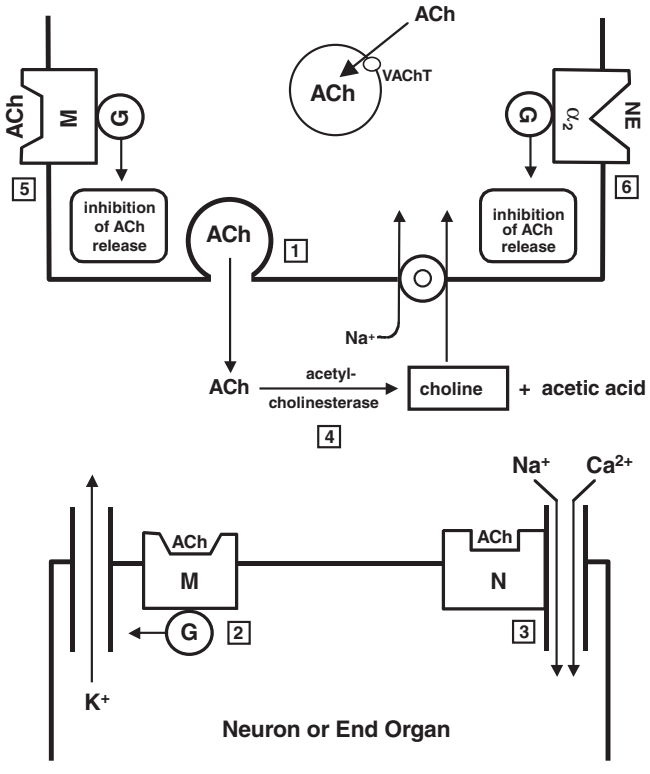

FIG. 14–2. Cholinergic nerve ending. Activation of postsynaptic muscarinic receptors hyperpolarizes the postsynaptic membrane through G-protein–mediated enhancement of K^+ efflux. Several subtypes of muscarinic receptors coupled to various G proteins exist—a muscarinic receptor coupled to a G protein that opens K^+ channels is shown only as an example. Postsynaptic nicotinic receptor activation causes Na^+ influx and membrane depolarization. Importantly, Ca^{2+} influx appears to be the main cation involved with some neuronal nicotinic receptors. Presynaptic muscarinic an α_2-adrenoreceptor activation prevents ACh release through lowering of intracellular Ca^{2+} concentrations. The agents listed in Table 14–1 may act to enhance or prevent release of ACh [1]; activate or antagonize postsynaptic muscarinic (M) receptors [2]; activate or antagonize nicotinic (N) receptors [3]; inhibit acetylcholinesterase [4]; prevent ACh release by stimulating presynaptic muscarinic autoreceptors [5] or α_2-adrenergic heteroreceptors [6]; or enhance ACh release by antagonizing presynaptic autoreceptors [5] or by antagonizing presynaptic α_2-adrenergic heteroreceptors [6] (on parasympathetic postganglionic terminals). ACh = acetylcholine; G = G protein; NE = norepinephrine; VAChT = vesicular transporter of ACh.

renal gland, acting as a modified sympathetic ganglion, releases epinephrine and lesser amounts of norepinephrine in response to stimulation of neuronal nAChRs. Epinephrine-containing neurons also reside in the brainstem.

TABLE 14–1. Examples of Xenobiotics That Affect Cholinergic Neurotransmission

Cholinomimetics	Cholinolytics
Cause ACh release	Direct nicotinic antagonists
α_2-Adrenergic antagonists[a]	α-Bungarotoxin[c]
Aminopyridines	Coniine
Black widow spider venom	Cytisine
Carbachol	Gallamine
Guanidine	Hexamethonium
	Lobeline
Anticholinesterases	Mecamylamine
Echothiophate iodide	Nicotine
Edrophonium	Nondepolarizing neuromuscular blocking agents
Galantamine	Succinylcholine[b]
N-methylcarbamate insecticides	Trimethaphan
Metrifonate	
Neostigmine	
Organic phosphorus insecticides	Indirect neuronal nicotinic antagonists
Physostigmine	Physostigmine
Pyridostigmine	Tacrine
Rivastigmine	Galantamine
Tacrine	
Direct nicotinic agonists	Direct muscarinic antagonists
Carbachol	Amantadine
Coniine	Antihistamines
Cytisine	Atropine
Lobeline	Benztropine
Nicotine	Carbamazepine
Succinylcholine (initial)[b]	Clozapine
	Cyclobenzaprine
Indirect neuronal nicotinic agonists	Disopyramide
Chlorpromazine	Glutethimide
Corticosteroids	Orphenadrine
Ethanol	Phenothiazines
Ketamine	Procainamide
Local anesthetics	Quinidine
Phencyclidine	Scopolamine
Volatile anesthetics	Tricyclic antidepressants
	Trihexyphenidyl
Direct muscarinic agonists	
Arecoline	Inhibit ACh release
Bethanechol	α_2-Adrenergic agonists[d]
Carbachol	Botulinum toxins
Methacholine	Crotalidae venoms
Muscarine	Elapidae β-neurotoxins
Pilocarpine	Hypermagnesemia

ACh = acetylcholine.
[a]Antagonism of α_2-adrenoceptors enhances ACh release from parasympathetic nerve endings.
[b]Depolarizing neuromuscular blocking agent.
[c]α-Bungarotoxin exemplifies many elapid α-neurotoxins that produce paralysis and death from respiratory failure.
[d]Stimulation of presynaptic α_2-adrenoceptors on parasympathetic nerve endings prevents ACh release.

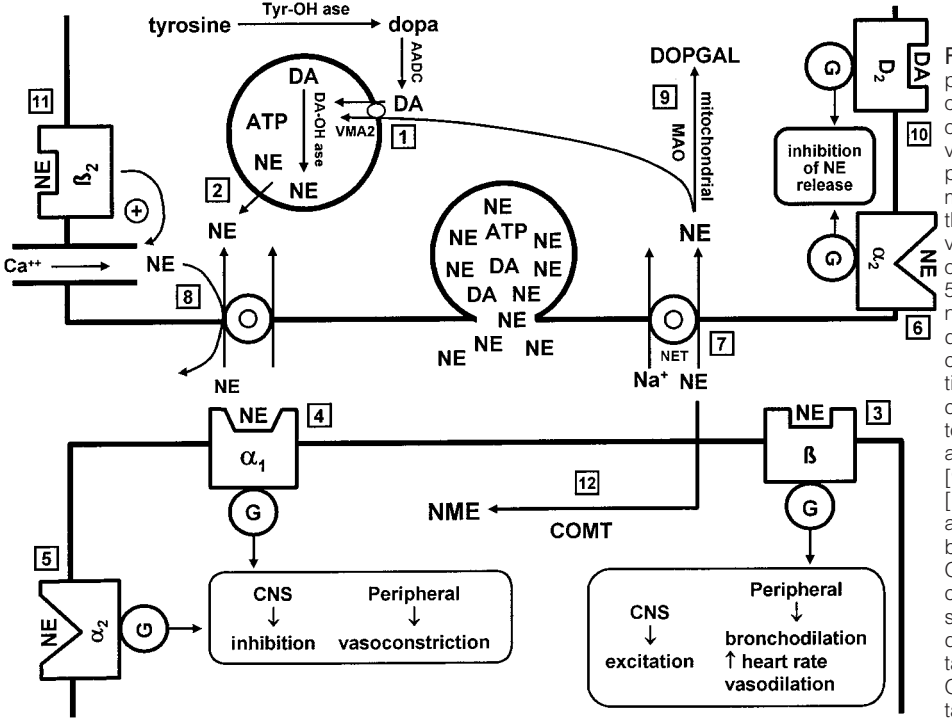

FIG. 14–3. Noradrenergic nerve ending. The postsynaptic membrane may represent an end organ or another neuron I the CNS. Brief examples of effects resulting from postsynaptic receptor activation are shown. Agents in Tables 14–2 and 14–3 produce effects by inhibiting transport of dopamine (DA) or norepinephrine (NE) into vesicles through VMA2 [1]; causing movement of NE from vesicles into the cytoplasm [2]; activating or antagonizing postsynaptic α- and β-adrenoreceptors [3–5]; modulating NE release by activating or antagonizing presynaptic α_2-autoreceptors [6], dopamine$_2$ (D_2) heteroreceptors [10], or β_2-autoreceptors [11]; blocking uptake of NE (NET inhibition) [7]; causing reverse transport of NE from the cytoplasm into the synapse via NET by raising cytoplasmic NE concentrations [8]; inhibiting monoamine oxidase (MAO) to prevent NE degradation [9]; or inhibiting COMT to prevent NE degradation [12]. COMT is not found in neurons in large amounts. AADC = aromatic L-amino acid decarboxylase; ATP = adenosine triphosphate; DA-OHase = dopamine-β-hydroxylase; COMT = catechol-*O*-methyltransferase; CNS = central nervous system; DOPGAL = 3,4-dihydroxyphenylglycoaldehyde; G = G protein; NET = membrane NE uptake transporter; NME = normetanephrine; tyr-OHase = tyrosine hydroxylase; VMA2 = vesicle uptake transporter for NE.

Synthesis, Release, and Uptake

Tyrosine hydroxylase is the rate-limiting enzyme in norepinephrine synthesis and is sensitive to negative feedback by norepinephrine. About one-half of cytoplasmic dopamine is actively pumped into vesicles containing the enzyme dopamine-β-hydroxylase. The remaining dopamine is quickly deaminated. In the vesicle, dopamine is converted to norepinephrine by dopamine-β-hydroxylase. In neurons containing epinephrine as a neurotransmitter, norepinephrine is released from vesicles into the cytoplasm, where it is converted to epinephrine and transported back into vesicles before synaptic release.

Norepinephrine is removed from the synapse mainly by uptake into the presynaptic neuron by the norepinephrine transporter (NET). Although this transporter has great affinity for norepinephrine, it also transports other amines, including dopamine, tyramine, monoamine oxidase inhibitors (MAOIs), and amphetamines. Once pumped back into the cytoplasm, norepinephrine can either be transported back into vesicles for further storage and release, or can be quickly enzymatically degraded by monoamine oxidase (MAO). Neuronal MAO degrades cytoplasmic amines to prevent elevated cytoplasmic concentrations. Hepatic and intestinal MAO prevent large quantities of dietary bioactive amines from entering the circulation.

Adrenergic Receptors

The two main types of adrenoceptors are α-adrenoceptors and β-adrenoceptors. β-Adrenoceptors are divided into three major subtypes (β_1, β_2, and β_3), depending on their affinity for various agonists and antagonists. In general, peripheral β_1-adrenoceptors are found mainly in the heart (along with β_2-receptors), whereas peripheral β_2-adrenoceptors, which are found mainly in the lungs and blood vessels, also mediate additional adrenergic effects. Presynaptic β_2-adrenoceptor activation causes release of norepinephrine. β_3-Adrenoceptors reside mainly in fat, where they regulate metabolic processes. α-Adrenoceptors inhibit adenylate cyclase and lower cyclic adenosine monophosphate (cAMP) levels, affect ion channels, increase intracellular calcium through inositol triphosphate and diacylglycerol production, or produce other actions. Stimulation of peripheral α-adrenergic receptors commonly results in vasoconstriction. Presynaptic α_2-adrenoceptor activation mediates negative feedback, limiting further release of norepinephrine. Postganglionic parasympathetic neurons (cholinergic) also contain presynaptic α_2-adrenoceptors that, when stimulated, prevent release of ACh. Postsynaptic α_2-adrenoceptors on vasculature mediate vasoconstriction.

Chemical Agents

Xenobiotics producing pharmacologic effects that result in or mimic increased activity of the adrenergic nervous system are *sympathomimetics* (Table 14–2). Those with the opposite effect are *sympatholytics* (Table 14–3). Xenobiotics whose sympathomimetic actions result from direct binding to α- or β-adrenoceptors are called *direct acting*. Those that produce sympathomimetic effects by almost any other mechanism are called indirect-acting sympathomimetics.

Dopamine

Dopamine is the direct precursor of norepinephrine. In contrast to the diffuse projections of noradrenergic neurons, dopaminergic neurons and receptors are

TABLE 14–2. EXAMPLES OF SYMPATHOMIMETICS

Direct acting	Selective α_2-adrenoceptor
β-Adrenoceptor agonists	antagonists
Albuterol	Idazoxan
Dobutamine	Yohimbine
Epinephrine	
Isoproterenol	Imidazoline binding-site antagonists
Metaproterenol	Idazoxan
Norepinephrine	
Ritodrine	MAOIs
Terbutaline	Amphetamine metabolites
	Clorgyline[a]
α-Adrenoceptor agonists	Isocarboxazid
Dobutamine	Linezolid
Epinephrine	Moclobemide[a]
Ergot alkaloids	Pargyline
Methoxamine	Phenelzine
Norepinephrine	Selegiline[b]
Phenylephrine	Tranylcypromine
Indirect acting	Inhibit NE uptake
Amphetamines	Amphetamines
Cocaine	Atomoxetine
Fenfluramine	Benztropine
MAOIs	Bupropion
Methylphenidate	Carbamazepine
Pemoline	Cocaine
Phencyclidine	Diphenhydramine
Phenmetrazine	Duloxetine
Propylhexedrine	Orphenadrine
Tyramine	Pemoline
	Reboxetine
Mixed acting	Tramadol
Dopamine	Tricyclic antidepressants
Ephedrine	Trihexyphenidyl
Mephentermine	Venlafaxine
Phenylpropanolamine	
Pseudoephedrine	

MAOIs = monoamine oxidase inhibitors; NE = norepinephrine.
[a]Mainly inhibit MAO-A at low doses.
[b]Mainly inhibit MAO-B at low doses.

highly organized and concentrated in several areas, especially in the basal ganglia and limbic system. In peripheral tissues, dopamine receptors cause vasodilation of mesenteric and coronary vascular beds. Dopamine can also stimulate β-adrenoceptors and, at high doses, can directly stimulate α-adrenoceptors. When dopamine is administered intravenously, most vasoconstriction is caused by dopamine-induced norepinephrine release.

Excessive dopaminergic activity in the neostriatum may produce acute choreoathetosis and acute Gilles de la Tourette syndrome, with tics, spitting, and cursing. Excessive dopaminergic activity in the limbic system produces paranoid psychosis and is thought responsible for drug craving and addictive behavior. Diminished dopaminergic tone produces various extrapyramidal disorders, such as acute dystonias and parkinsonism.

TABLE 14–3. Examples of Sympatholytics

α-Adrenoceptor antagonists	Penbutolol[a]
Clozapine	Pindolol[a]
Doxazosin	Practolol[a]
Droperidol	Propranolol
Ergot alkaloids	Sotalol
Labetalol	Timolol
Olanzapine	
Phenothiazines	Prevent NE release with depolarization
Phenoxybenzamine	Bretylium[b]
Phentolamine	Reserpine[b]
Prazosin	
Quinidine	α_2-Adrenoceptor agonists[d]
Risperidone	α-Methyldopa[c]
Terazosin	Brimonidine
Tolazoline	Clonidine
Trazodone	Dexmedetomidine
Tricyclic antidepressants	Guanabenz
Urapidil	Guanfacine
	Moxonidine
Inhibit dopamine-β-hydroxylase	Naphazoline
Diethyldithiocarbamate	Oxymetazoline
Disulfiram	Rilmenidine
MAOIs	Tetrahydralazine
	Xylometazoline
β-Adrenoceptor antagonists	
Acebutolol[a]	Imidazoline binding-site agonists[d]
Alprenolol[a]	Clonidine
Atenolol	Guanabenz
Betaxolol	Guanfacine
Bisoprolol	Moxonidine
Carteolol	Naphazoline
Carvedilol	Oxymetazoline
Esmolol	Rilmenidine
Labetalol	
Metipranolol[a]	Inhibitors of vesicle uptake
Metoprolol	Reserpine[b]
Nadolol	Tetrabenazine
Oxprenolol[a]	

NE = norepinephrine; MAOIs = monoamine oxidase inhibitors.
[a]Partial β-agonist.
[b]Causes transient NE release after initial dose.
[c]Metabolized to α-methylnorepinephrine, which activates α_2-receptors.
[d]Agents in these categories vary in their relative selectivity for α_2-adrenoceptors or imidazoline binding sites.

Synthesis, Release, and Uptake

The steps of dopamine synthesis and vesicle storage are the same as those for norepinephrine, except that dopamine is not converted to norepinephrine after transport into vesicles. Dopamine is removed from the synapse via uptake by a membrane-bound dopamine transporter that is capable of transporting other structurally similar sympathomimetics. Cytoplasmic dopamine has a fate similar to norepinephrine.

Dopamine Receptors

Dopamine receptors are divided into two main groups, depending on whether they raise or lower cAMP concentrations. Dopamine D_1-like receptors (D_1 and D_5) raise cAMP concentrations; D_2-like receptors (D_2, D_3, D_4) lower concentrations of cAMP. D_2 receptors are concentrated in the basal ganglia and limbic system. D_3 receptors are concentrated in the hypothalamic and limbic nuclei, whereas D_4 receptors are concentrated in the frontal cortex and limbic nuclei (rather than basal ganglia nuclei).

Chemical Agents

Table 14–4 provides common examples of xenobiotics that affect dopaminergic neurotransmission.

Serotonin

Serotonin (5-HT, 5-OH-tryptamine) is a ubiquitous compound found in nature (animals, plants, venoms) that is also an endogenous neurotransmitter. In the CNS, serotonergic neurons project to virtually all areas of the brain. Serotonin is involved with mood, personality, affect, appetite, motor function, temperature regulation, sexual activity, pain perception, sleep induction, and other basic functions. Serotonin is not essential for any of these processes, but modulates their quality and extent. The serotonergic system is extremely diverse, with 14 types of receptors described.

Peripherally, 5-HT is produced mainly in the enterochromaffin cells of the intestine. Local release contributes to peristalsis. Platelets take up 5-HT while passing through the enteric circulation. Serotonin is released from activated platelets to interact with other platelet membranes (promote aggregation) and with vascular smooth muscle (vasoconstriction in most vascular beds).

Centrally, 5-HT definitely plays an important role in the action of many hallucinogenic drugs, which act as partial agonists at cortical 5-HT_2 receptors. Proserotinergic agents are used to treat depression, whereas agents that antagonize 5-HT receptors (5-HT_2) have taken on greater importance in the management of schizophrenia.

Synthesis, Release, and Uptake

Tryptophan-5-hydroxylase is the rate-limiting enzyme of 5-HT synthesis and is free from negative feedback influences by 5-HT. Thus increases in tryptophan are predictably accompanied by increased 5-HT production. L-Amino acid decarboxylase (dopa decarboxylase) converts 5-hydroxytryptophan to 5-HT. Cytoplasmic 5-HT is transported into vesicles, where it is concentrated by ion trapping before release by Ca^{2+}-dependent exocytosis. After release into the synapse, a transporter in the neuronal membrane transfers 5-HT back into the neuron, where it reenters vesicles or is degraded by MAO.

Serotonin Receptors

There are seven major receptors (5-HT_1 through 5-HT_7) and numerous subtypes. Only subclasses 5-HT_1 through 5-HT_3 are currently sufficiently understood to implicate them in specific clinical effects. Excessive stimulation of

TABLE 14–4. Examples of Xenobiotics That Affect Dopaminergic Neurotransmission

Dopamine agonism
Direct stimulation of dopamine receptors
Apomorphine
Bromocriptine
Cabergoline
L–Dopa[a]
Fenoldopam
Lisuride
Pergolide
Pramipexole
Ropinirole
Inhibit dopamine metabolism—MAOIs
Clorgyline
Isocarboxazid
Linezolid
Moclobemide
Pargyline
Phenelzine
Selegiline
Tranylcypromine
Inhibit dopamine metabolism—COMTs
Entacapone
Tolcapone
Indirect acting
Amantadine
Amphetamines
Benztropine
Decongestants
Diphenhydramine
MAOIs
Methylphenidate
Orphenadrine
Pemoline
Phencyclidine
Trihexyphenidyl
Inhibit dopamine uptake
Amantadine
Amphetamines
Benztropine
Bupropion
Cocaine
Diphenhydramine
Methylphenidate
Orphenadrine
Pemoline
Trihexyphenidyl
Increase dopamine receptor sensitivity
Amphetamines
Antipsychotics
Metoclopramide
Phenytoin
Dopamine antagonism
Block dopamine receptors
Amoxapine
Buspirone
Clozapine
Droperidol
Haloperidol
Loxapine
Metoclopramide
Molindone
Olanzapine
Phenothiazines
Pimozide
Quetiapine
Risperidone
Thioxanthenes
Trazodone
Tricyclic antidepressants[b]
Ziprasidone
Destroy dopaminergic neurons
MPTP
Prevent vesicle dopamine uptake
Reserpine
Tetrabenazine

COMTs = catechol-*O*-methyltransferase inhibitors; MAOIs = monoamine oxidase inhibitors; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.
[a]Metabolized to dopamine, which acts as an agonist.
[b]Relatively weak D_2-receptor antagonists.

5-HT_{1A} receptors and, to a lesser extent, 5-HT_2 receptors, causes serotonin syndrome.

5-HT$_1$ Receptors Cranial blood vessels (eg, meninges) possess 5-HT_{1D} and 5-HT_{1B} receptors, whose activation produces vasoconstriction and decreased inflammation.

5-HT$_2$ Receptors The three subtypes of 5-HT_2 receptors are so similar in characterization that investigational agents have great difficulty in distinguishing the subtypes. 5-HT_{2A} receptors are most concentrated in the cerebral cortex, where they serve as excitatory postsynaptic receptors. Activation of 5-HT_{2B} receptors in the GI tract promotes colonic contraction.

5-HT$_3$ Receptors These receptors are especially concentrated in the chemoreceptive triggering zone, where their activation induces emesis. Cortical 5-HT_3 receptors are frequently identified on γ-aminobutyric acid (GABA) interneurons where they increase inhibitory, GABAergic tone. In contrast to cerebral actions, activation of peripheral 5-HT_3 receptors on cholinergic nerves in the gut enhances ACh release to increase gastrointestinal motility.

Chemical Agents

Table 14–5 provides common examples of xenobiotics that affect serotonergic neurotransmission.

γ-Aminobutyric Acid

GABA is one of two main inhibitory neurotransmitters of the CNS (glycine is discussed below). GABA agonists are generally used as anticonvulsants, sedative-hypnotics, and general anesthetics. GABA antagonists typically produce CNS excitation and convulsions. GABA is synthesized from glutamate, the brain's main excitatory neurotransmitter.

Synthesis, Release, and Uptake

Glutamic acid decarboxylase, which converts glutamate to GABA, requires pyridoxal phosphate as a cofactor. Pyridoxal phosphate is synthesized from pyridoxine (vitamin B_6) by the enzyme pyridoxine kinase. A vesicle-bound transporter transports GABA into vesicles from where it is released through Ca^{2+}-dependent exocytosis. Uptake of GABA from the synapse is mediated by a Na^+-dependent transporter. In glial cells, cytoplasmic GABA can undergo degradation by GABA-transaminase to succinic semialdehyde, part of which then undergoes oxidation to succinate.

GABA Receptors

There are two main types of GABA receptors. $GABA_A$ receptors are Cl^- channels that mediate postsynaptic inhibition. The $GABA_B$ receptor is found on both pre- and postsynaptic membranes and mediates both presynaptic and postsynaptic inhibition. A third, poorly defined, GABA receptor, $GABA_C$, is a Cl^- channel that, when activated, allows increases Cl^- influx.

Chemical Agents

Table 14–6 provides common examples of xenobiotics that affect GABAergic neurotransmission.

TABLE 14–5. Examples of Xenobiotics That Affect Serotonergic Neurotransmission

- Serotonin agonism
  - Enhance 5-HT synthesis
    - L-Tryptophan
    - 5-Hydroxytryptophan
  - Direct 5-HT agonists
    - Buspirone
    - Cisapride
    - Ergots and indolesa
    - Flesinoxan
    - Gepirone
    - Hallucinogenic substituted amphetamines
    - Ipsapirone
    - mCPP
    - Mescaline[a]
    - Metoclopramide
    - Naratriptan
    - Renzapride
    - Rizatriptan
    - Sulpiride
    - Sumatriptan
    - Tandospirone
    - Tegaserod
    - Urapidil
    - Zacopride
    - Zolmitriptan
  - Increase 5-HT release
    - Amphetamines
    - Cocaine
    - Codeine derivatives
    - Dexfenfluramine
    - Dextromethorphan
    - L-Dopa
    - Fenfluramine
    - MDMA
    - Mirtazapine
    - Reserpine (initial)
  - Increase 5-HT tone by unknown mechanism
    - Lithium
  - Inhibit 5-HT breakdown (MAOIs)
    - Clorgyline
    - Isocarboxazid
    - Linezolid
    - Moclobemide
    - Pargyline
    - Phenelzine
    - Tranylcypromine
    - Selegiline
  - Inhibit 5-HT Uptake
    - Citalopram
    - Cocaine
    - Dextromethorphan
    - Duloxetine
    - Escitalopram
    - Fluoxetine
    - Fluvoxamine
    - Lamotrigine
    - Meperidine
    - Milnacipran
    - Nefazodone
    - Reboxetine
    - Sertraline
    - Tramadol
    - Trazodone
    - Tricyclic antidepressants[b]
    - Venlafaxine
- Serotonin antagonism
  - Direct 5-HT antagonists
    - Alosetron
    - Amisulpride
    - Clozapine
    - Cyproheptadine
    - Dolasetron
    - Ergots and indoles (eg, LSD)[a]
    - Granisetron
    - Haloperidol
    - Ketanserin
    - Mianserin
    - Mescaline[a]
    - Methysergide
    - Metoclopramide
    - Mirtazapine
    - Nefazodone
    - Olanzapine
    - Ondansetron
    - Phenothiazines
    - Phentolamine
    - Pindolol
    - Propranolol
    - Quetiapine
    - Risperidone
    - Ritanserin
    - Sertindole
    - Trazodone
    - Tricyclic antidepressants
    - Tropisetron
    - Ziprasidone
    - Zotepine
  - Enhance 5-HT uptake
    - Tianeptine

(continued)

TABLE 14–5. Examples of Xenobiotics That Affect Serotonergic Neurotransmission *(continued)*

Inhibit 5-HT uptake	Inhibit vesicle uptake
Amoxapine	Ketanserin
Amphetamines	Reserpine
Atomoxetine	Tetrabenazine
Carhamazenine	

5-HT = serotonin; LSD = lysergic acid diethylamide; MAOIs = monoamine oxidase inhibitors; mCPP = *m*-chlorophenylpiperazine (metabolite of trazodone and nefazodone); MDMA = methylenedioxymethamphetamine.
[a]Indoles and phenylalkylamines activate and antagonize various 5-HT receptors. Their hallucinogenic/illusionogenic effects mainly result from partial agonism at 5-HT_2 receptors.
[b]Clomipramine is the most potent 5-HT uptake inhibitor of the tricyclic antidepressants.

TABLE 14–6. Examples of Xenobiotics That Affect GABAergic Neurotransmission

GABA agonism	GABA antagonism
Stimulate GAD	Direct $GABA_A$ antagonists
Gabapentin	Bicuculline
Valproate	Cephalosporins
	Ciprofloxacin
Direct $GABA_A$ agonists	Enoxacin
Muscimol	Imipenem
Progabide[a]	Nalidixic acid
	Norfloxacin
Indirect $GABA_A$ agonists	Ofloxacin
Avermectin	Penicillins
Barbiturates	
Benzodiazepines	Indirect $GABA_A$ antagonists
Chloral hydrate	Aztreonam
Clomethiazole	Clozapine
Ethanol	Flumazenil
Etomidate	Lindane
Felbamate	MAOIs
Ivermectin	Maprotiline
Meprobamate	Organochlorine insecticides
Methaqualone	Penicillins
Propofol	Pentylenetetrazol
Steroids	Picrotoxin
Topiramate	Tricyclic antidepressants
Trichloroethanol	
Volatile anesthetics	Inhibit GAD
Zaleplon	Cyanide
Zolpidem	Domoic acid
Zopiclone	Hydrazines
	Isoniazid
Direct $GABA_B$ agonists	
Baclofen	Direct $GABA_B$ antagonists
GHB	Phaclofen[b]
Progabide[a]	Saclofen[b]

(continued)

TABLE 14–6. Examples of Xenobiotics That Affect GABAergic Neurotransmission *(continued)*

Inhibit GABA-T	Inhibit PK
Vigabatrin	Hydrazines[c]
	Isoniazid[c]
Inhibit GABA uptake	
Guvacine	
Tiagabine	
Valproate	

GABA = γ-aminobutyric acid; GABA-T = GABA transaminase; GAD = glutamic acid decarboxylase; GHB = γ-hydroxybutyric acid; PK = pyridoxine kinase; MAOIs = monoamine oxidase inhibitors.
[a]Directly activate $GABA_A$ and $GABA_B$ receptors as well as being metabolized to GABA.
[b]Thought not to cross blood–brain barrier in meaningful amounts.
[c]Major site of action is PK inhibition, though some direct GAD inhibition occurs.

GLYCINE

Glycine acts as a postsynaptic inhibitory neurotransmitter in the spinal cord and lower brainstem. In the CNS, serine is converted to glycine by serine hydroxymethyltransferase (SHMT).

Release and Uptake

Glycine is transported into storage vesicles and undergoes exocytosis upon neuronal depolarization. Glycine is removed from the synapse through uptake by a Na^+-dependent transporter into presynaptic neurons and into glial cells.

Glycine Receptors

Like $GABA_A$, the glycine receptor is a Cl^- channel on the postsynaptic membrane that stimulates an inward Cl^- current and hyperpolarizes the cell membrane.

Chemical Agents

Table 14–7 provides examples of xenobiotics that affect inhibitory glycine Cl^- channels.

Table 14–7.
Examples of Xenobiotics That Affect Inhibitory Glycine Chloride Channels

Glycine agonists	Glycine antagonists
Ethanol	Strychnine
Propofol	Picrotoxin
D-Serine	Glycine uptake inhibitor
	Clozapine

Ethanol and propofol enhance Cl^- influx through glycine Cl^- channels, although they do not appear to act as direct agonists. Evidence exists for picrotoxin's direct antagonism at the glycine binding site(s) in contrast to $GABA_A$ Cl^- channels, where it acts at a site separate from where GABA (γ-aminobutyric acid) binds.

GLUTAMATE

Glutamate is the main excitatory neurotransmitter in the CNS. Although glutamate receptor stimulation is necessary for normal brain activity, excessive glutamate receptor activation can produce convulsions, neuronal damage, and death. Conversely, glutamate antagonists demonstrate anticonvulsant activity and neuroprotective action in animal models of brain and spinal cord injury. Glutamate may be important in the development of drug abuse and subsequent withdrawal symptoms. Glutamate antagonists decrease drug craving and withdrawal symptoms in patients dependent on ethanol, benzodiazepines, and opioids.

Synthesis, Release, and Uptake

Glutamate is primarily synthesized from glutamine and released from vesicles by Ca^{2+}-dependent exocytosis. Glutamate undergoes uptake both by neuronal and glial cells. Synaptic glutamate transported into glial cells undergoes conversion back to glutamine, which is released back into the synapse for uptake and recycling back to glutamate and then into storage vesicles. Glutamate also serves as the precursor for GABA's synthesis.

Glutamate Receptors

The excitatory amino acid receptor system is the most complex of all neurotransmitter systems. This complexity is necessary for protection against the devastating effects of uncontrolled excitatory neurotransmission. At present, 11 different glutamate receptors are recognized. Three are cation channels, and 8 metabotropic receptors are linked to G proteins.

Ionotropic Glutamate Receptors

Three ionotropic glutamate receptors have been identified. They are named by their abilities to be activated or antagonized by various substances: kainate, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate), and NMDA (*N*-methyl-D-aspartate).

The NMDA receptor is a Ca^{2+} channel whose activation allows for inward Ca^{2+} and Na^{+} currents (and some K^{+} efflux), resulting in neuronal depolarization and excitation. Antagonists demonstrate anticonvulsant and neuroprotective activity during times of neuronal insult, as calcium influx contributes to accumulation of intracellular calcium and cell damage. Excessive activation of glutamate receptors has the potential to produce neuronal cytotoxicity. The NMDA Ca^{2+} channel is blocked by Mg^{2+} in a voltage-dependent manner, preventing Ca^{2+} influx despite glutamate binding.

Metabotropic Glutamate Receptors

Metabotropic glutamate receptors are linked to various G proteins on post- and presynaptic membranes. Eight different receptors have been isolated that either excite or inhibit at postsynaptic membranes, and appear mainly to inhibit at presynaptic locations.

Chemical Agents

Table 14–8 provides examples of xenobiotics that affect glutamatergic neurotransmission.

TABLE 14–8. Examples of Xenobiotics That Affect Glutamatergic Neurotransmission

Glutamate agonism	NMDA receptor antagonists
Direct glutamate receptor agonists	Amantadine
BMAA	Dextrorphan
BOAA	Dizocilpine (MK801)
Domoic acid	Ketamine
Ibotenic acid	Memantine
Willardine	Orphenadrine
	Pentamidine
Glycine NMDA receptor agonists	Phencyclidine
D-Cycloserine	Ethanol[a]
Milacemide	
	NMDA glycine antagonists
Glutamate uptake inhibitor	Felbamate
Clozapine	Kynurenic acid
	Meprobamate
Glutamate antagonism	
Prevent glutamate release	Polyamine antagonists
Lamotrigine	Eliprodil
Nimodipine	Ifenprodil
Riluzole	

BMAA = α-amino-β-methylaminopropionic acid; BOAA = β-*N*-oxalylamino-L-alanine; NMDA = *N*-methyl-D-aspartate.
[a]Ethanol antagonizes glutamate's action at NMDA receptors through an unknown mechanism.

ADENOSINE

The overall action of adenosine throughout the body is to lessen oxygen requirements and to increase oxygen and substrate delivery. Thus adenosine functions in the CNS as an extremely important inhibitory neuromodulator and vasodilator.

Synthesis, Release, and Uptake

A Na^+-dependent purine uptake transporter moves adenosine into the neuron. During times of adequate oxygen delivery and oxidative phosphorylation, intracellular adenosine triphosphate (ATP) concentrations are normally manyfold greater than those of adenosine. Adenosine begins conversion to ATP by adenosine kinase, but adenosine can also be metabolized to inosine by adenosine deaminase, a less important pathway.

ATP is commonly coreleased with other neurotransmitters (eg, norepinephrine, ACh, glutamate) into the synapse where it can be degraded to adenosine monophosphate (AMP). When oxygen delivery remains adequate to meet metabolic demands, most synaptic adenosine arises from the extracellular dephosphorylation of AMP.

During times of inadequate oxygen delivery, intracellular adenosine concentrations rapidly rise as phosphorylated adenosine species are degraded to adenosine. The rise in intracellular adenosine concentration results in reverse transport of adenosine into the synapse by the purine uptake transporter. Synaptic adenosine, then, activates adenosine receptors on neuronal and nonneuronal tissue (eg, vasculature). The actions of adenosine are terminated by uptake into glial cells and neurons.

TABLE 14–9. Examples of Xenobiotics That Affect Adenosine Receptors

Adenosine agonism	Inhibit ADA
Direct agonists	Acadesine
Adenosine	Dipyridamole
ADAC (adenosine amine congener)	Pentostatin
Tecadenoson	
	Inhibit AK
Inhibit uptake	Acadesine
Acadesine	
Acetate[a]	Increase adenosine release
Benzodiazepines	Opioids
Calcium channel blockers	
Carbamazepine	Adenosine antagonism
Dipyridamole	A_1 blockade
Ethanol[a]	Caffeine
Flumazenil	Carbamazepine
Indomethacin	Theophylline
Papaverine	
Propentofylline	A_2 blockade
Tricyclic antidepressants	Caffeine
	Theophylline

ADA = adenosine deaminase; AK = adenosine kinase.
[a]Ethanol is metabolized to acetate, which inhibits adenosine uptake.

Adenosine Receptors

The purine P_1 receptor family comprises four adenosine receptor subtypes linked to G proteins: A_1, A_{2A}, A_{2B}, and A_3. Postsynaptic A_1 stimulation results in K^+ channel opening and K^+ efflux with subsequent hyperpolarization of the neuron. Presynaptic A_1 stimulation modifies voltage-dependent Ca^{2+} channels, lessening Ca^{2+} influx during depolarization, which limits exocytosis of neurotransmitter. Therefore, activation of A_1 receptors prevents release of neurotransmitters presynaptically and inhibits their response postsynaptically.

A_1 receptor stimulation also produces sedation and is important in sleep regulation. Other functions attributed to A_1 receptors include neuroprotection, anxiolysis, temperature reduction, anticonvulsant activity, and spinal analgesia. Peripheral A_1 receptor activation produces bronchoconstriction, decreased glomerular filtration, decreased heart rate, slowed atrioventricular conduction, and decreased atrial myocardial contractility. In the CNS, A_{2A} receptors are produced in cerebral vasculature and produce vasodilatation when stimulated. Additionally, A_{2A} receptors are especially prevalent on neurons in the striatum where they inhibit the activity of D_2 receptors. A_{2B} receptors produce cerebral and coronary artery vasodilation.

Chemical Agents

Table 14–9 provides examples of xenobiotics that affect adenosine receptors.

15 Withdrawal Principles

In the CNS, excitatory neurons fire regularly, and inhibitory neurons inhibit the transmission of these impulses. Whenever action is required, the inhibitory tone diminishes, permitting the excitatory nerve impulses to travel to their end organs. Thus, all action in human neurophysiology is disinhibition.

Tonic activity of a xenobiotic produces an adaptive change in the neuron. For example, tonic stimulation of an inhibitory neuron reduces the activity of that neuron so that the baseline level of function is again attained. A withdrawal syndrome occurs when the constant presence of this xenobiotic is removed or reduced and the adaptive changes persist. This produces a dysfunctional state in which there is significantly reduced inhibitory neurotransmission, essentially producing excitation. Every withdrawal syndrome has two characteristics: (a) a preexisting physiologic adaptation to a xenobiotic, the continuous presence of which prevents withdrawal; and (b) decreasing concentrations of that xenobiotic. In contrast, simple tolerance to a drug is characterized as a physiologic adaptation that shifts the dose-response curve to the right. That is, greater amounts of xenobiotic are required to achieve a given effect. Patients with withdrawal syndromes often have developed tolerance, but tolerance does not require the continued presence of the xenobiotic to prevent withdrawal. Figure 15–1 demonstrates this process schematically.

The *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition* (DSM-IV) provides a helpful and descriptive set of criteria that mesh with our understanding of the pathophysiology of withdrawal syndromes. According to DSM-IV, withdrawal is manifested by either of the following: (a) a characteristic withdrawal syndrome for the substance, or (b) the same (or a closely related) substance is taken to relieve withdrawal symptoms. Note that either criterion fulfills this definition. Logically, all syndromes have the first criteria, and so it is the presence of the second criteria that is critical to understanding physiology and therapy.

For the purposes of defining a unifying pathophysiology of withdrawal syndromes, this chapter considers syndromes in which both features are present. An analysis from this perspective distinguishes xenobiotics that affect the inhibitory neuronal pathways from the effects of those agents that stimulate the excitatory neuronal pathways, such as cocaine. Cocaine does not produce a withdrawal syndrome using this definition, but rather a postintoxication syndrome that often results in lethargy, hypersomnolence, movement disorders, and irritability. This syndrome does not meet the second feature of the DSM-IV criteria for a withdrawal syndrome, because the same (or a closely related) substance is not taken to relieve or avoid withdrawal symptoms. This postintoxication syndrome, the so-called "crack crash" or "washed-out syndrome," is caused by prolonged use of the drug, and patients return to their premorbid function without intervention. This distinction is important for toxicologists, because (a) withdrawal syndromes that demonstrate both features of the DSM-IV criteria are treated with reinstatement and gradual withdrawal of a substance that has an effect on the receptor and (b) withdrawal syndromes that do not demonstrate the second feature require only supportive care and resolve spontaneously.

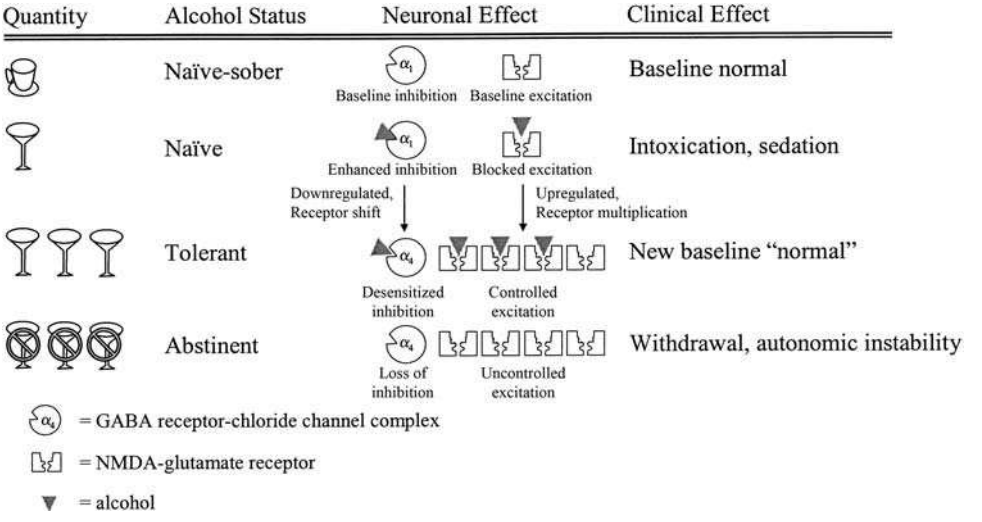

FIG. 15–1. Alcohol intoxication, tolerance, and withdrawal. Alcohol consumption in alcohol-naive persons produces intoxication and sedation by simultaneous agonism at the γ-aminobutyric acid (GABA) receptor-chloride channel complex and antagonism at the *N*-methyl-D-aspartate (NMDA)-glutamate receptor. Continuous alcohol consumption leads to the development of tolerance through changes in both the GABA receptor-chloride channel complex (a subunit shift from α_1 to α_4 results in reduced sensitivity to the sedating effects of alcohol) and the NMDA subtype of glutamate receptor (upregulation in number, resulting in enhanced wakefulness). There is conceptually a level at which the tolerant patient may appear clinically normal despite having an elevated blood alcohol concentration. Tolerant patients who are abstinent lose the tonic effects of alcohol on these receptors, resulting in withdrawal.

Finally, withdrawal syndromes are best described and treated based on the class of receptors that are affected because this concept also organizes the approach to patient care. For each receptor and its agonists, research has identified genomic and nongenomic effects that produce neuroadaptation and withdrawal syndromes. There appear to be 6 mechanisms involved: (a) genomic mechanisms via messenger ribonucleic acid (mRNA); (b) second-messenger effects via protein kinases, cyclic adenosine monophosphate (cAMP), and calcium ions; (c) receptor endocytosis; (d) expression of various receptor subtypes depending on location within the synapse (synaptic localization); (e) intracellular signaling via effects on other receptors; and (f) neurosteroid modulation. All or some of these mechanisms are already demonstrated in each of the known withdrawal states. These mechanisms develop in a surprisingly rapid fashion and modify the receptor and its function in such complex ways so as to depend on the continued presence of the substance to prevent dysfunction.

$GABA_A$ RECEPTORS (BARBITURATES, BENZODIAZEPINES, ETHANOL, VOLATILE SOLVENTS)

γ-Aminobutyric acid type A ($GABA_A$) receptors have separate binding sites for GABA, barbiturates, benzodiazepines, and picrotoxin, to name a few (Chap. 14). Barbiturates and benzodiazepines bind to separate receptor sites and enhance the affinity for $GABA_A$ at its receptor site. $GABA_A$ receptors are part of a superfamily of ligand-gated ion channels, including nicotinic acetylcholine receptors and glycine receptors, which exist as pentamers arranged around a central ion channel. When activated, they hyperpolarize the postsynaptic neuron by facilitating an inward chloride current (without a G-protein messenger), decreasing the likelihood of the neuron firing an action potential.

The GABA receptor is a pentamer comprised of two α subunits, two β subunits, and an additional subunit, most commonly γ, which is a key element in the benzodiazepine binding site. The two GABA binding sites per receptor are located in a homologous position to the benzodiazepine site between the α and β subunits. Although the mechanism is unclear, benzodiazepines have no direct functional effect without the presence of GABA. Conversely, certain barbiturates, or perhaps all in a dose-dependent manner, can increase the duration of channel opening, producing a net increase in current flow without GABA binding.

Recent evidence demonstrates that this prototypical pentameric $GABA_A$ receptor assembly is derived from a permutation and combination of 2, 3, 4, or even 5 different subunits. The subtypes of GABA receptors can even vary on the same cell. In fact, GABA receptors are heterogeneous receptors with different subunits and distinct regional distribution. Although the preponderance of subtypes $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, and $\alpha_3\beta_3\gamma_2$ account for 75% of GABA receptors, there are at least 16 others of importance. The recognition of additional subunits of $GABA_A$ receptors, such as ω, has permitted the development of targeted pharmaceuticals. For example, zolpidem achieves its effect of hastened onset of sleep by targeting the ω_1 receptor subunit of $GABA_A$.

Previously ethanol was thought to have GABA-receptor activity, although a clearly identified binding site was not evident (Chap. 75). Traditional explanations for this effect include (a) enhanced membrane fluidity and allosteric potentiation (so-called cross-coupling) of the 5 proteins that construct the $GABA_A$ receptor; (b) interaction with a portion of the receptor; and/or (c) en-

hanced GABA release. Research with chimeric reconstruction of $GABA_A$ and *N*-methyl-D-aspartate (NMDA) channels demonstrates highly specific binding sites for high doses of ethanol which enhance $GABA_A$ and inhibit NMDA receptor-mediated glutamate neurotransmission. However, research has not clarified whether ethanol at low doses is a direct agonist of $GABA_A$ receptors or a potentiator of $GABA_A$ receptor binding.

Ethanol exhibits all 6 mechanisms of adaptation to chronic exposure and is the prototypical substance for studying neuroadaptation and withdrawal. These 6 mechanisms appear to apply to benzodiazepines as well. The mechanisms are (a) altered $GABA_A$ receptor gene expression via alterations in mRNA and peptide levels of $GABA_A$ receptor subunits in numerous regions of the brain (genomic mechanisms); (b) posttranslational modification through phosphorylation of receptor subunits with protein kinase C (second-messenger effects); (c) subcellular localization by an increased internalization of $GABA_A$ receptor α_1-subunit receptors (receptor endocytosis); (d) modification of receptor subtypes with differing affinities for agonists to the synaptic or nonsynaptic sites (synaptic localization); (e) regulation via intracellular signaling by the NMDA, acetylcholine, serotonin, and β-adrenergic receptors; and (f) neurosteroid modulation of GABA receptor sensitivity and expression.

Intracellular signaling via the NMDA subtype of the glutamate receptor appears to explain the "kindling" hypothesis, in which successive withdrawal events become progressively more severe. The activity of an excitatory neurotransmission increases the more it fires, a phenomenon known as long-term potentiation, and is the result of increased activity of mRNA and receptor protein expression—a genomic effect of intracellular signaling. As NMDA receptors increase in number and function (upregulation), and $GABA_A$ receptor activity diminishes, withdrawal becomes more severe. The dizocilpine (MK-801) binding site of the NMDA receptor appears to be the major contributor, and this effect is recognized in neurons that express both NMDA and $GABA_A$ receptors. Interestingly, animal models suggest that chronic ethanol use induces alterations in the receptor subunit composition of the $GABA_A$ receptor, and this may be partly responsible for the development of ethanol tolerance, withdrawal, and kindling.

In summary, it is an oversimplification to view $GABA_A$ receptors as a homogenous and static collection of cell-surface proteins that are stimulated by sedatives. $GABA_A$ agonists induce modulatory changes in the receptors through genomic and nongenomic mechanisms that ultimately alter their function. In this way, withdrawal symptoms represent the clinical manifestation of a change in GABA-receptor-complex characteristics. When alcohol or any drug with GABA-agonist activity is withdrawn, inhibitory control of excitatory neurotransmission, such as that mediated by the now upregulated NMDA receptors, is lost. This results in the clinical syndrome of withdrawal: CNS excitation (tremor, hallucinations, seizures) and autonomic stimulation (tachycardia, hypertension, hyperthermia, diaphoresis) (Chap. 76).

Volatile solvents are widespread substances of abuse that appear to be mediated by the GABA receptor. Examples include gasoline, ether, and toluene, and all have a well-established abuse potential, especially in adolescents. These chemicals can produce CNS inhibition and anesthesia at escalating doses via the $GABA_A$ receptor. Elaboration of the mechanism specific for solvent abuse awaits further study, although it is logical to assume it acts in a similar fashion as ethanol and other drugs with the $GABA_A$ receptor. It also appears to use the same dopamine reward system as other drugs of abuse.

$GABA_B$ RECEPTORS (GHB AND BACLOFEN)

$GABA_B$ agonists such as γ-hydroxybutyric acid (GHB) display similar clinical characteristics of adaptation and withdrawal. The $GABA_B$ receptor is a heterodimer of the $GABA_{B(1)}$ and $GABA_{B(2)}$ receptors. Unlike $GABA_A$, the $GABA_B$ receptor couples to various effector systems through a signal-transducing G protein. $GABA_B$ receptors mediate presynaptic inhibition (by preventing Ca^{2+} influx) and postsynaptic inhibition (by increasing K^+ efflux). The postsynaptic receptors appear to have a similar inhibitory effect as the $GABA_A$ receptors. The presynaptic receptors provide feedback inhibition of GABA release. Unlike $GABA_A$ receptors, these are mediated through G-protein messengers.

GHB is a naturally occurring inhibitory neurotransmitter with its own distinct receptor. Physiologic concentrations of GHB activate at least 2 subtypes of a distinct GHB receptor (antagonist-sensitive and antagonist-insensitive). However, at supraphysiologic concentrations such as those that occur after overdose and abuse, GHB also binds directly to the $GABA_B$ receptor and is also metabolized to GABA (which then activates the $GABA_B$ receptor). Endogenous GHB activates a presynaptic GHB receptor to modulate GABA and glutamate release and inhibits dopamine release by the $GABA_B$ receptor. The GHB withdrawal syndrome clinically resembles the withdrawal syndrome noted from ethanol and benzodiazepines. Distinctive clinical features of GHB withdrawal are the relatively mild and brief autonomic instability with the persistence of psychotic symptoms.

Baclofen is also a $GABA_B$ agonist. The pre- and postsynaptic inhibitory properties of baclofen allow it, paradoxically, to cause seizures in both acute overdose (as a result of decreased release of presynaptic $GABA_B$ via $GABA_B$ autoreceptors) and withdrawal. Withdrawal is probably a result of the loss of chronic inhibitory effect of baclofen on postsynaptic $GABA_B$ receptors. Upon discontinuation, this produces hyperactivity of neuronal Ca^{2+} channels (N, P/Q type), leading to seizures, hypertension, hallucinations, psychosis, and coma. However, these manifestations may not differ from the withdrawal symptoms of $GABA_A$ agonists.

Typically, the development of a baclofen withdrawal syndrome occurs 24–48 hours after discontinuation of baclofen. Case reports highlight the development of seizures, hallucinations, psychosis, dyskinesias, and visual disturbances. The intrathecal baclofen pump is an effective replacement for oral dosing, but withdrawal can occur following use of this modality as well. Reinstatement of the prior baclofen dosing schedule appears to resolve these symptoms within 24–48 hours. Benzodiazepines and $GABA_A$ agonists, not phenytoin, are the appropriate treatment for seizures induced by baclofen withdrawal.

OPIOID RECEPTORS (OPIATES AND OPIOIDS)

Similar to ethanol and $GABA_A$ receptors, opioid binding to the opioid receptors result in a series of genomic and nongenomic neuroadaptations—especially via second-messenger effects. Opioids inhibit neurons and alleviate pain when they bind to an opioid receptor, activate G_s proteins, and stimulate K^+ efflux currents. The opioid receptors are also linked to the $G_{i/o}$ proteins. These act through adenyl cyclase and activate inward Na^+ current, thus enhancing the intrinsic excitability of a neuron (Chap. 38).

Chronic exposure to opiates and opioids (all drugs with opioid-receptor affinity) results in a decrease in efficacy of this receptor to open potassium channels by genomic mechanisms and second-messenger effects. Following

chronic opioid exposure, the expression of adenyl cyclase increases through activation of the transcription factor known as cyclic adenosine monophosphate response element-binding protein (CREB). This results in an upregulation of cAMP-mediated responses such as the inward Na^+ channels responsible for intrinsic excitability. The net effect is that only higher levels of opioids result in analgesia and opioid effect. In the dependent patient, when opioid levels drop, inward Na^+ flux occurs unchecked, and the patient experiences the opioid withdrawal syndrome. The clinical findings associated with this syndrome are largely due to uninhibited activity at the locus ceruleus.

Furthermore, opioid receptors and central α_2-adrenergic receptors both exert a similar effect on the potassium channel in the locus coeruleus. Clonidine binds to the central α_2-adrenergic receptor and stimulates potassium efflux, as do opioids, and produces similar clinical findings. This explains why clonidine has some efficacy in treating the opioid withdrawal syndrome. In addition, the antagonistic effect of naloxone at the opioid receptor seems to reverse the effect of clonidine on this shared potassium efflux channel.

Rapid opioid detoxification is a form of iatrogenic withdrawal that uses drugs with antagonist activity to accelerate a return to premorbid receptor states. In theory, inducing opioid withdrawal under general anesthesia with high-dose opioid antagonists permits the transition from drug dependency to naltrexone maintenance without drug withdrawal symptoms. Naltrexone blocks the euphoric effects of continued opioid use and discourages recidivism by blunting drug craving. Although the mechanism by which naloxone blocks drug craving is not entirely understood, the speculation is that mere receptor occupancy by an antagonist is sufficient to blunt cravings. However, withdrawal symptoms may still be intense and can persist for up to 1 week after rapid detoxification, suggesting that clinical recovery from the changes induced by chronic opioid use is slow.

α_2-ADRENERGIC RECEPTORS (CLONIDINE)

α_2-Adrenergic receptors are located in the central and peripheral nervous system. Clonidine is a central and peripheral α_2-adrenergic agonist. Stimulation of central presynaptic α_2-adrenergic receptors inhibits sympathomimetic output and results in bradycardia and hypotension. Within 24 hours after the discontinuation of chronic clonidine use, norepinephrine levels rise as a result of enhanced efferent sympathetic activity. This results in hypertension, tachycardia, anxiety, diaphoresis, and hallucinations.

ADENOSINE (A) RECEPTORS (CAFFEINE)

The release of neurotransmitters is accompanied by passive release of adenosine as a by-product of adenosine triphosphate (ATP) breakdown. The released adenosine binds to postsynaptic A_1 receptors where it typically has inhibitory effects on the postsynaptic neuron. It also binds to presynaptic A_1 autoreceptors to limit further release of neurotransmitters. A_2 receptors are found on the cerebral vasculature and peripheral vasculature where stimulation promotes vasodilation. Caffeine and other methylxanthines, such as theophylline, antagonize the inhibitory effect of adenosine, primarily on postsynaptic A_1 receptors. As a result, acute exposure results in increases in heart rate, ventilation, gastrointestinal motility, gastric acid secretion, and motor activity. Chronic caffeine exposure results in tolerance to the clinical effects of large, acute doses of caffeine. Chronic caffeine exposure regulates

A_1 receptors by a variety of mechanisms, such as increases in receptor number, increases in receptor affinity, enhancing receptor coupling to the G protein, and increases in G-protein–stimulated adenyl cyclase. An animal study demonstrates that the adenosine receptor has a 3-fold increase in affinity for adenosine at the height of withdrawal symptoms. This model suggests that chronic caffeine administration results in increase in receptor affinity for adenosine, thus restoring a state of physiologic balance (normal motor inhibitory tone). When caffeine is withdrawn, the enhanced receptor affinity results in a strong adenosine effect and clinical symptoms of withdrawal: headache (cerebral vasodilation), fatigue, and hypersomnia (motor inhibition).

ACETYLCHOLINE RECEPTORS (NICOTINE)

Nicotinic receptors are a type of acetylcholine receptor located in the autonomic ganglia, adrenal medulla, CNS, spinal cord, neuromuscular junction, and carotid and aortic bodies. Nicotinic receptors are fast-response cation channels that are not coupled to G proteins, distinguishing them from muscarinic receptors, which are coupled to G proteins. Nicotinic acetylcholine receptors have both excitatory and inhibitory effects. As in other withdrawal syndromes, changes brought on by chronic use of nicotinic agonists, such as nicotine in cigarettes, appear to be related to selective upregulation of cAMP. Much remains unknown about these receptors and how they affect addiction and withdrawal.

SELECTIVE SEROTONIN REUPTAKE INHIBITOR DISCONTINUATION SYNDROME

Evidence supports that upon discontinuation of chronic selective serotonin reuptake inhibitor (SSRI) therapy, patients develop a syndrome. This syndrome complies with the definition of withdrawal syndromes in that symptoms begin when drug concentrations drop and reinstatement of the drug abates the syndrome. Most case reports point to venlafaxine as the most common drug involved in this syndrome. Headache, nausea, fatigue, dizziness, and dysphoria are commonly described symptoms. The condition appears to be uncomfortable but not life-threatening, and rapidly resolves with reinstatement of a drug of the same class and resolves when the drug is discontinued after a more gradual taper (Chap. 70).

Section II. Pathophysiologic Basis: Organ Systems

16 | Thermoregulatory Principles

Despite exposure to wide fluctuations of environmental temperature, human body temperature is maintained within a narrow range. Elevation or depression of body temperature occurs when (a) thermoregulatory mechanisms are overwhelmed by exposure to extremes of environmental heat or cold; (b) endogenous heat production is either inadequate, resulting in hypothermia, or exceeds the physiologic capacity for dissipation, resulting in hyperthermia; or (c) disease processes or drug effects interfere with normal thermoregulatory responses to heat or cold exposure.

METHODS OF HEAT TRANSFER

Heat is transferred to or away from the body through radiation, conduction, convection, and evaporation. *Radiation* involves the transfer of heat from a body to the environment, and from warm objects in the environment, for example, the sun, to a body. *Conduction* involves the transfer of heat to solid or liquid media in direct contact with the body. Water immersion or wet clothing in contact with the body conducts significant amounts of heat away from the body. This effect facilitates cooling in a swimming pool on a hot summer day, or may lead to hypothermia despite moderate ambient temperatures on a rainy day. The amount of heat lost through conduction and radiation depends on the temperature gradient between skin and surroundings, cutaneous blood flow, and insulation, such as subcutaneous fat, hair, clothing, or, in lower animals, fur. *Convection* is the transfer of heat to the air surrounding the body. Wind velocity and ambient air temperature are the major determinants of convective heat loss. *Evaporation* is the process of vaporization of water, or sweating. Large amounts of heat are dissipated from the skin during this process, resulting in cooling. Ambient temperature, rate of sweating, air velocity, and relative humidity are important factors in determining how much heat is lost through evaporation. On a very humid day, sweat may pour off, rather than evaporate from a person exercising in a hot environment, thereby accomplishing little heat loss. In very warm environments, thermal gradients may be reversed, leading to transfer of heat to the body by radiation, conduction, or convection.

PHYSIOLOGY OF THERMOREGULATION

In the normal human, stimulation of peripheral and hypothalamic temperature-sensitive neurons results in autonomic, somatic, and behavioral responses that lead to the dissipation or conservation of heat. Thermoregulation is the complex physiologic process that serves to maintain hypothalamic temperature within a narrow range of 98.6 ± 0.8°F (37 ± 0.4°C) known as the set point. Maintaining, raising, or lowering the hypothalamic set point results in many outwardly visible

physiologic manifestations of thermoregulation, such as sweating, shivering, flushing, or panting.

NEUROTRANSMITTERS AND THERMOREGULATION

The neurotransmitters involved in thermoregulation include serotonin, norepinephrine, acetylcholine, dopamine, prostaglandins, β-endorphins, and intrinsic hypothalamic peptides such as arginine vasopressin, adrenocorticotropic hormone, thyrotropin-releasing hormone, and α-melanocyte–stimulating hormone. Studies on the effects of individual neurotransmitters in thermoregulation yield contradictory results, depending on the animal species and the route of administration of the exogenous neurotransmitter.

HYPOTHERMIA

Hypothermia is defined as an unintentional lowering of the core body temperature to <95°F (<35°C). Between 1979 and 2002, 16,555 people died of hypothermia in the United States, an average of 689 per year. Medical factors increase the risk in the elderly, including limited mobility, impaired shivering, chronic illness, confusion, decreased protective fat, and slower metabolic rates. Social isolation and deprivation, poor nutrition, and inadequate access to or use of indoor heating, often because of financial concerns, are additional factors associated with the development of hypothermia. Other risks associated with hypothermia in all groups are ethanol use, mental illness, use of antipsychotic medication, hypothyroidism, starvation, immobilization, dehydration, poverty, and homelessness.

Response to Cold

The normal physiologic response to cold is initiated by stimulation of cold-sensitive neurons in the skin, so that the onset of the body's response to cold occurs prior to cooling of central blood. Cold-sensitive neurons in the skin send afferent impulses to the hypothalamus, resulting in shivering and piloerection. Shivering is the main thermoregulatory response to cold in humans, except in neonates, in whom nonshivering thermogenesis prevails. Nonshivering thermogenesis is mediated by the sympathetic nervous system through mobilization of fat and glucose stores (β-adrenergic receptors). In humans, brown fat is found primarily in neonates, although in cold-acclimatized people there may be small amounts found on autopsy. Brown adipose tissue functions as a thermoregulatory effector organ, producing heat by the oxidation of fatty acids when the tissue is stimulated by norepinephrine.

Disease Processes and Hypothermia

Several disease processes commonly result in an inability to maintain a normal body temperature in a cool environment. Hypothermia may develop in association with sepsis, hypothyroidism, hypoglycemia, uremia, hepatic failure, or poor nutrition (eg, thiamine deficiency).

Evaluations to determine the presence of underlying diseases are often difficult in the hypothermic patient. The mental status may be markedly altered by hypothermia but is not usually abnormal until the temperature falls below 90°F (32.2°C). If a normal mental status is not regained when the temperature reaches 90°F (32.2°C) during rewarming, underlying CNS structural, toxic, or metabolic problems must be considered. Failure of the patient to rewarm quickly suggests the presence of underlying disease. In one study, hypothermic patients without underlying disease were reported to rewarm at a rate of 1.0–3.7°F/h (0.6–2.1°C/h)

(average: 2.1°F/h; 1.2°C/h), whereas patients with significant underlying disease (sepsis, gastrointestinal hemorrhage, diabetic ketoacidosis, pulmonary embolus, myocardial infarction) warmed at a rate of 0.25–1.8°F/h (0.1–1.0°C/h) (average: 1°F/h; 0.6°C/h).

Clinical Findings

The clinical effects of hypothermia are related to the membrane-depressant effects of cold, which result in ionic and electrical conduction disturbances in the brain, heart, peripheral nerves, and other major organs (Table 16–1).

TABLE 16–1. Physiologic and Clinical Manifestations of Hypothermia

Cardiovascular
Normal, decreased, or increased cardiac output
Normal heart rate or tachycardia, then bradycardia
Vasoconstriction and central shunting of blood
ECG
Prolongation of intervals
Atrial fibrillation
Increased ventricular irritability
J-point elevation "Osborn waves"
Central nervous system
Mild: 90–95°F (32–35°C)
Normal mentation or slightly slowed
Moderate: 80–90°F (27–32°C)
Lethargic but verbally responsive
Severe: 68–80°F (20–27°C)
Unlikely to respond verbally, purposefully to noxious stimuli
Profound: <68°F (<20°C)
Unresponsive, may appear dead
Gastrointestinal tract
Decreased motility
Depressed hepatic metabolism
Hematologic
Hemoconcentration
Left shift of oxyhemoglobin dissociation curve
Kidneys
Cold-induced diuresis
Antidiuretic hormone antagonism
Lungs
Respiratory rate variable
Bronchorrhea
Metabolic
Metabolic acidosis
Increased glycogenolysis
Increased serum free fatty acids
Normal thyroid and adrenal function

Effects on the CNS are temperature-dependent and predictable. Mild hypothermia (90–95°F [32.2–35°C]) usually results in relatively benign clinical manifestations. Ataxia, slight clumsiness, slowed response to stimuli, and dysarthria are common. As cooling continues, the mental status slowly deteriorates. In moderate hypothermia (80–90°F [27–32.2°C]), the patient is usually lethargic but still likely to respond verbally. In severe hypothermia (68–80°F [20–26.6°C]), the patient is unlikely to respond verbally but will react purposefully to noxious stimuli. In profound hypothermia (<68°F [20°C]), the patient is unresponsive to stimuli. Pupils may be fixed and dilated and the patient may appear dead. However, standard criteria of brain death do not apply to hypothermic patients. Under controlled circumstances patients have survived with temperatures as low as 48.2°F (9°C). Vigorous resuscitation is required for these patients.

The cardiac and hemodynamic effects of cold correlate closely with body temperature. As cooling begins there is a transient increase in cardiac output. Tachycardia develops secondary to shivering and sympathetic stimulation. At about 81°F (27.2°C) shivering ceases. Bradycardia develops with maintenance of a normal cardiac stroke volume, although in profound hypothermia, bradycardia may progress to asystole and death.

The Electrocardiogram

The most common ECG abnormality in hypothermia is generalized, progressive depression of myocardial conduction. Heart rate and PR, QRS, and QTc are all prolonged, and increasingly profound hypothermia may lead to gradual progression to asystole. Ventricular fibrillation occurs in an irritable myocardium most commonly at temperatures less than 86°F (30°C). Atrial fibrillation is the most common dysrhythmia occurring in the presence of hypothermia. Shivering may not be clinically evident, but a fine muscular tremor frequently produces a mechanical artifact in the baseline of the electrocardiogram. A deflection occurring at the junction of the QRS and ST segment, known as the *Osborn wave*, is invariably present in patients with temperatures <86°F (<30°C) (see Fig. 16–1).

Management

The hypothermic patient should be given 0.5–1.0 g dextrose/kg body weight as $D_{50}W$ and 100 mg of thiamine IV. If hypoglycemia is the cause of the hypothermia, the response to dextrose may be dramatic, heralded by the onset of shivering and a rapid return to normal body temperature. If clinically indicated for airway protection, or inadequate ventilation, or oxygenation, endotracheal intubation should cautiously be performed, although there is a risk of ventricular fibrillation occurring during endotracheal intubation. Every effort should be made to limit patient activity and stimulation during the acute rewarming period, as activity may increase myocardial oxygen demand or alter myocardial temperature gradients, increasing the risk of iatrogenic ventricular fibrillation. Central venous lines should be avoided unless absolutely essential, so as not to precipitate ventricular dysrhythmias. Patients who develop ventricular fibrillation are difficult to manage. In these instances, cardiopulmonary resuscitation (CPR) should be initiated, and the patient intubated and ventilated to maintain a pH of 7.40 uncorrected for temperature. Active internal rewarming should be instituted because standard therapy for ventricular fibrillation is often unsuccessful until rewarming is achieved. Pa-

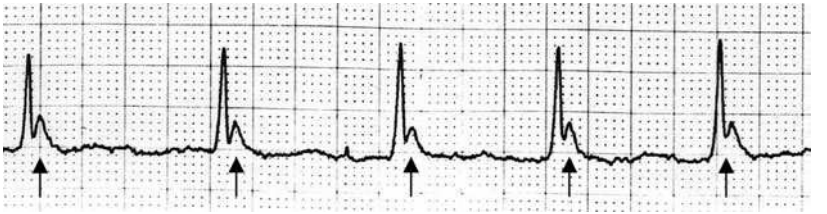

FIG. 16–1. A characteristic electrocardiographic finding in the patient with profound hypothermia. The terminal phase of the QRS complex shows a typical elevation of the J-point Osborn wave (↑).

tients should be supported, then defibrillated; if unsuccessful, defibrillation should not be attempted again until the patient has been warmed several degrees centigrade. Defibrillation may not be successful until the temperature exceeds 86°F (30°C) The pneumatically powered "thumper" and cardiopulmonary bypass devices are used successfully during prolonged hypothermic cardiopulmonary arrests. Blood-gas values of pH and PCO_2 should be left uncorrected after the blood sample is warmed in the blood-gas machine and interpreted in the same way as in the normothermic patient.

Pharmacologic Interventions

To expand intravascular volume, 0.9% sodium chloride solution should be given. Urine output is an important indicator of organ perfusion and the adequacy of intravascular volume in the hypothermic patient, although the initial cold diuresis may lead to underestimation of fluid needs. After the administration of intravenous fluids, dopamine infusion is indicated in the patient requiring blood pressure support.

The best means to effect resuscitation of the hypothermic victim in ventricular fibrillation is controversial. The most recent recommendations for the treatment of cardiac arrest when the body core temperature is <86°F (<30°C) does not include the administration of a vasopressor drug or antidysrhythmic. There are no data to support this. There are data, however, that suggest the possibility of improved chance of resuscitation with the use of antidysrhythmics. The administration of vasopressin to pigs in hypothermic cardiac arrest increases coronary perfusion pressure and improved defibrillation success, although it does not improve long-term outcome.

The role of antidysrhythmics such as amiodarone or bretylium is undefined. Given the difficulty of treating ventricular fibrillation once it occurs during hypothermia, the preponderance of evidence suggests a role for the use of bretylium. However, bretylium has been removed from the American Heart Association guidelines for advanced cardiac life support and may no longer be available in some institutions.

Rewarming

Three types of rewarming modalities are used in the management of hypothermic patients. *Passive external rewarming* involves covering the patient with blankets and protecting the patient from further heat loss. Passive external rewarming uses the patient's own endogenous heat production for rewarming and is most successful in healthy patients with mild to moderate hypothermia whose capacity for endogenous heat production is intact. *Active external rewarming* involves the external application of heat to the patient. Acute vasodilation of peripheral vessels could cause hypotension and an increased peripheral demand on the persistently cold myocardium. *Afterdrop* is the continuing decrease in temperature once rewarming begins. Some authors (including the American Heart Association Advanced Cardiac Life Support [ACLS] guidelines) recommend that rewarming of the extremities should be delayed by application of heat to the trunk only, rather than to the trunk and extremities, in an attempt to avoid the complications of afterdrop and intramyocardial temperature gradients. In our experience, active external rewarming has not been associated with mortality except in those patients with severe underlying disease.

Active internal rewarming involves attempts to increase central core temperature directly, by warming the heart prior to the extremities or periphery.

The administration of heated, humidified oxygen delivered by face mask is considered part of active internal rewarming. Additional minimally invasive modalities of active internal rewarming include endotracheal intubation with warmed, humidified oxygen, and gastric lavage with warmed fluids. Extracorporeal methods of active internal rewarming should be reserved for severely hypothermic patients (<80°F or <27°C) or those with unstable cardiac rhythms (ventricular fibrillation or tachycardia, or asystole) attributed to hypothermia. The evidence for the benefit of extracorporeal methods in those patients with stable rhythms is not yet available. In patients with stable rhythms, studies are essential to resolve the debate over the merits of passive or active external rewarming versus active internal rewarming.

HYPERTHERMIA

Hundreds of people die annually of heatstroke in the United States, and 80% of the victims are older than age 50 years. Several studies show mortality rates from heatstroke to be 5.6–80%.

Heatstroke is defined as a rectal temperature greater than 106°F (41.1°C) in the setting of a neurologic disturbance manifested by psychosis, delirium, stupor, coma, and/or convulsions. Temperature criterion cannot be absolute, as information regarding the patient's temperature is rarely available at the time of onset of heatstroke. Although the absence of sweating was once thought to be an essential component of the definition of heatstroke, many patients with heatstroke maintain the ability to sweat on presentation.

Thermoregulation and Heat Stress

The normal thermoregulatory response to heat stress is mediated primarily by heat-sensitive neurons in the hypothalamus. Increased body core temperature results in active dilatation of cutaneous vessels, and skin blood flow increases. Increased skin blood flow is attained primarily by an increase in heart rate and stroke volume; therefore, the capacity to increase cardiac output is critical to cooling. Compensatory shifting of blood flow from the splanchnic and renal vessels to the skin further increases skin blood flow. Sweat-gland function is activated by sympathetic stimulation, and the combination of vasodilation, increased skin blood flow, and increased sweating results in heat loss through convection and evaporation. Dehydration after profuse sweating increases plasma osmolarity.

Types of Heatstroke

Heatstroke is commonly divided into two types: exertional and nonexertional. Nonexertional, or classic, heatstroke describes heatstroke occurring in the absence of extreme exertion. Nonexertional heatstroke is most commonly described during heat waves, and the victims are predominantly those persons least able to tolerate heat: infants, the aged, those with psychiatric disorders, and the chronically ill.

Exertional heatstroke occurs as a result of increased motor activity. It may occur in young, healthy individuals who are exercising, or in individuals whose increased motor activity results from other causes, such as seizures or agitation. Often a period of significant heat stress in exercising individuals precedes the development of heatstroke. Symptoms of nausea, weakness, headache, diarrhea, or irritability often precede the development of heatstroke. Although rapid onset of symptoms and acute loss of consciousness are frequently reported in exertional

TABLE 16–2. Differential Diagnosis of Hyperthermia

I. Increased heat production
- *Increased muscle activity*
  - Agitation
  - Catatonia
  - Ethanol withdrawal
  - Exercise
  - Infectious diseases
  - Malignant hyperthermia
  - Monoamine oxidase inhibitor drug interactions
  - Neuroleptic malignant syndrome
  - Parkinson disease
  - Sedative-hypnotic withdrawal
  - Seizures
  - Serotonin syndrome
  - Xenobiotics
- *Increased metabolic rate*
  - Hyperthyroidism
  - Pheochromocytoma
  - Sympathomimetics

II. Impaired heat loss
- *Environmental*
  - Heat
  - Humidity
  - Lack of acclimatization
- *Social disadvantage*
  - Isolation
  - Poverty
  - Lack of air conditioning
  - Confinement to bed
- *Medical illness*
  - Cardiac insufficiency
  - Diabetes
  - Hypertension
  - Pulmonary
  - CNS dysfunction
- *Dehydration*
- *Fatigue*
- *Limited behavioral response*
  - Extremes of age
  - Psychiatric impairment
  - Mental retardation
  - Xenobiotics

heatstroke, the preceding period of heat stress and insidious symptoms may go unrecognized. Although exertional heatstroke is more likely to occur during intense exertion in a hot, humid environment, it may also occur with moderately intense exercise early in the morning, when environmental conditions do not usually represent a thermoregulatory stress (Table 16–2).

Clinical Findings in Heatstroke

Clinical evaluation of the hyperthermic patient begins with careful assessment of the vital signs. Vital sign abnormalities commonly include tachycar-

dia, hypotension, and an elevation of the respiratory rate, often above 30 breaths/min. After cooling, there is often a secondary rise in temperature that suggests persistent disturbances of thermoregulation (Table 16–3).

Neurologic examination reveals a confused, delirious, comatose, or seizing patient. Pupils may be normal, fixed and dilated, or pinpoint. Decerebrate or decorticate posturing may be evident. Muscle tone is increased, normal, or flaccid. The skin may be hot and dry or diaphoretic. Nasal and oropharyngeal bleeding may be present as a consequence of the acute coagulopathy. Examination of the lungs is often nonspecific, although heatstroke victims are at risk of pulmonary edema as a primary event associated with capillary endothelial damage or following overly aggressive fluid resuscitation. Cardiac auscultation may reveal a flow murmur secondary to high cardiac output or a right ventricular gallop. Neck vein distension indicates increased central venous pressure. Jaundice suggests hepatic injury and occurs on the second or third day following the onset of heatstroke. Nasogastric aspiration or rectal examination may demonstrate gross bleeding. A petechial rash develops, probably secondary to capillary endothelial damage.

Laboratory Findings of Heatstroke

Lactic acid dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and muscle enzymes are typically elevated in patients with heatstroke. Nonspecific ST- and T-wave changes on ECG are common. Myocardial enzyme elevation occurs and correlates with ECG changes. Results of lumbar puncture are nonspecific, are often normal, or may demonstrate elevated cerebrospinal fluid (CSF) protein and lymphocytosis. Metabolic acidosis and hypokalemia are common.

Treatment of Heatstroke

Management must focus on the early recognition of hyperthermia. Body temperatures >106°F (41.1°C) place the patient at great risk for end-organ injury. Rapid cooling is the first priority and is associated with improved outcomes. Cooling that is delayed, allowing body temperatures to remain above 102.2°F (38.9°C) for more than 30 minutes, is associated with a high rate of morbidity and mortality. Cooling by covering in ice water lowers the core temperature faster than cooling by using evaporative spray.

Successful treatment requires adequate preparation. Equipment needed for rapid cooling, including fans, ice, and tubs for submersion, should always be readily available in the emergency department. En route to the hospital, the patient's clothes should be removed and the patient should be covered with ice and water-soaked sheets. Respiration and cardiovascular status should be stabilized and monitored. Oxygen should be administered. The cause of the heatstroke should be determined and appropriate measures initiated immediately. Pharmacologic agents, such as antihistamines, butyrophenones, and phenothiazines, and physical restraints that interfere with heat dissipation, such as camisoles and strait jackets, should not be used. Light hand and foot restraints should be used to protect the patient from harming himself or herself. The patient who is hyperthermic in the setting of ethanol or sedative-hypnotic withdrawal should be treated with a benzodiazepine. The patient should never be confined to a small, unventilated seclusion room. Adequate cooling, hydration, sedation, and electrolytes and substrate repletion should be ensured.

TABLE 16–3. Physiologic and Clinical Manifestations of Heatstroke

Cardiovascular
- Hypodynamic states in elderly
- Hyperdynamic states in young healthy individuals
- Electrocardiogram
  - Nonspecific
  - Widening of QRS because of an underlying abnormality (cocaine toxicity, hyperkalemia associated with rhabdomyolysis)

Central nervous system
- Altered mental status
  - Irritability, confusion, ataxia, seizures, coma
  - Weakness, dizziness, headache
  - Plantar extension, pupillary abnormalities, decorticate posturing
- EEG
  - Normal or diffuse slowing
- CSF
  - Normal or increased protein
  - Lymphocytosis

Gastrointestinal
- Vomiting, diarrhea, hematemesis

Hematologic
- Bleeding diathesis
  - Prolonged PT and PTT
  - Disseminated intravascular coagulation
  - Thrombocytopenia
  - Petechiae
  - Purpura
- Leukocytosis

Hepatic
- Hepatic insufficiency at 12–36 h
- Elevated AST, ALT, LDH

Metabolic
- Metabolic acidosis and respiratory alkalosis
- Electrolyte disturbance
  - Hypernatremia
  - Hypokalemia
  - Hypocalcemia
  - Hypophosphatemia

Muscle
- Rhabdomyolysis
- Elevated CPK

Renal
- Decreased renal perfusion
- Myoglobinuria
- Proteinuria
- Oliguria
- Acute tubular necrosis
- Interstitial necrosis

TABLE 16–4. Management of Heatstroke

Preparation
- Ice and cooling fans available in emergency department
- Monitor weather reports
- Alert media

On Arrival
- Rapid cooling
  - Clear airway and administer oxygen
  - Cover with ice and water-soaked sheets
  - Stabilize respiratory and cardiovascular status
  - Cool as rapidly as possible
- Intravenous access
  - 0.9% NaCl or lactated Ringer solution based on CVP or pulmonary artery catheter
  - Administration of dextrose 0.5–1.0 g/kg, and thiamine 100 mg
  - Benzodiazepines for agitation, shivering, seizures
- Continuous monitoring
  - Remove from ice bath at 101°F (38.3°C)
  - Watch for rebound hyperthermia
- Cautions
  - Antipsychotics may have serious adverse effects
  - Antipyretics do not work
  - Cooling blankets alone are inadequate

Administration of 0.5–1.0 g/kg body weight dextrose as $D_{50}W$ and 100 mg of thiamine should be considered. A rectal probe should be placed for continuous temperature monitoring. The patient should be immersed in an ice bath with a fan blowing over the patient if possible. In addition to the ice bath, iced gastric lavage might be effective.

Agitation, seizures, and cardiac dysrhythmias must be managed while cooling is accomplished. Benzodiazepines are the treatment of choice for agitation and seizures. Heatstroke patients may have significant volume needs, depending on the amount of fluid lost prior to the onset of heatstroke. Hypotension should be treated with fluids and cooling. Volume repletion should be monitored carefully by parameters such as blood pressure, pulse, central venous pressure, pulmonary wedge pressure, and urine output. As the temperature returns to normal, the hypotension may resolve if significant volume deficits are not present. In patients with myoglobinuria, an attempt should be made to increase renal blood flow and urine output. The use of sodium bicarbonate and mannitol in the prevention of acute tubular necrosis in these cases is controversial.

There is no role for antipyretic agents in the management of heatstroke. Aspirin and acetaminophen lower temperature by reducing the hypothalamic set point, which is only altered in a patient febrile from inflammation or endogenous pyrogens. Heatstroke, however, occurs when cooling mechanisms are overwhelmed, and the hypothalamic thermoregulatory set point is not disturbed.

Dantrolene sodium is the preferred drug only in the treatment of malignant hyperthermia (see Antidotes in Brief: Dantrolene Sodium). It acts directly on

skeletal muscle and either inhibits the release of calcium or increases calcium uptake through the sarcoplasmic reticulum. Its usefulness has not been demonstrated in other conditions associated with hyperthermia, and there is no evidence to support its administration for other conditions. No drug therapy should delay the institution of aggressive external cooling (Table 16–4).

17 Fluid, Electrolyte, and Acid–Base Principles

A meaningful analysis of fluid, electrolyte, and acid–base abnormalities must be based on the clinical characteristics of each patient. Essential information concerning extracellular fluid volume (ECFV), pathophysiology, and treatment may only be gained from the history and physical examination.

INITIAL PATIENT ASSESSMENT

History

Common manifestations of toxin exposure result in fluid losses through the respiratory system (hyperpnea and tachypnea), gastrointestinal tract (vomiting and diarrhea), skin (diaphoresis), and kidneys (polyuria). Patients with ECFV depletion may complain of dizziness, thirst, and occasionally polydipsia, and usually the patients can identify the source of fluid loss. A history of exposures to nonprescription and prescription medications, toxins, and alternative therapies may suggest the most likely electrolyte or acid–base abnormality.

Physical Examination

The vital signs are invariably affected by gross alterations in ECFV. Whereas hypotension and tachycardia may herald life-threatening ECFV depletion, an initial increase of the heart rate and a narrowing of the pulse pressure may be earlier findings. The addition of orthostatic pulse and blood pressure measurements provides a more meaningful determination of functional ECFV status. Hyperventilation may be caused by a primary respiratory stimulus or may be a response to a metabolic acidosis. Hypoventilation is usually associated with a primary depression of consciousness and respiration, and respiratory acidosis. The skin should be evaluated for turgor, moisture, and the presence or absence of edema. The physical findings associated with electrolyte abnormalities also are nonspecific. Multiple, concurrent electrolyte disorders can produce confusing clinical presentations, or patients may appear normal.

Rapid Diagnostic Tools

The electrocardiogram (ECG) is a useful tool for screening of some common electrolyte abnormalities. Unfortunately, because of poor sensitivity and moderate specificity, the test, in actuality, is of limited diagnostic value. A bedside assessment of urine specific gravity by dipstick analysis may provide valuable information about ECFV status. A high urine specific gravity (>1.015) signifies concentrated urine and is often associated with ECFV depletion. The urine dipstick is also useful for detecting ketones, which are often associated with diabetic ketoacidosis, salicylate poisoning, and alcoholic ketoacidosis. The urine ferric chloride test rapidly detects exposure to salicylates with a high sensitivity and specificity.

Laboratory Studies

A simultaneous determination of the venous serum electrolytes, blood urea nitrogen (BUN), glucose, and arterial or venous blood gases is adequate to determine

the nature of the most common acid–base, fluid, and electrolyte abnormalities. More complex clinical problems may require determinations of urine and serum osmolalities, urine electrolytes, serum ketones, serum lactate, and other tests.

ACID–BASE ABNORMALITIES

Definitions

The terms *acidosis* and *alkalosis* refer to processes that tend to change pH in a given direction. By definition a patient is said to have:

A *metabolic acidosis* if the patient's arterial pH is less than 7.40 and serum bicarbonate concentration ($[HCO_3^-]$) is less than 24 mEq/L. Because acidemia stimulates ventilation (respiratory compensation), metabolic acidosis is usually accompanied by a PCO_2 less than 40 mm Hg.

A *metabolic alkalosis* if the patient's arterial pH is greater than 7.40 and serum $[HCO_3^-]$ is more than 24 mEq/L. Because alkalemia inhibits ventilation (respiratory compensation), metabolic alkalosis is usually accompanied by a PCO_2 greater than 40 mm Hg.

A *respiratory acidosis* if the patient's arterial pH is less than 7.40 and partial pressure of carbon dioxide (PCO_2) is greater than 40 mm Hg. Because an elevated PCO_2 stimulates renal acid excretion and the generation of $[HCO_3^-]$ (renal compensation), respiratory acidosis is usually accompanied by a serum $[HCO_3^-]$ greater than 24 mEq/L.

A *respiratory alkalosis* if the patient's arterial pH is greater than 7.40 and PCO_2 is less than 40 mm Hg. Because a decreased PCO_2 decreases renal net acid excretion and increases the excretion of $[HCO_3^-]$ (renal compensation), respiratory alkalosis is usually accompanied by a serum $[HCO_3^-]$ less than 24 mEq/L.

The terms *acidemia* and *alkalemia* refer only to the resultant arterial pH of blood (acidemia referring to a pH <7.40, and alkalemia referring to a pH >7.40). It is important to note that under most circumstances a venous pH is an acceptable approximation of arterial pH.

Determining the Primary Acid–Base Abnormality

It is helpful to begin by determining whether the patient is acidemic or alkalemic based on the pH. Next determine whether the compensation of the primary acid–base disorder is appropriate or excessive. Overcompensation cannot occur. That is, if the primary process is metabolic acidosis, respiratory compensation tends to raise the pH toward normal, but never to greater than 7.40. As a rule, compensation for a primary acid–base disorder that is inadequate or excessive suggests the presence of a second primary acid–base disorder.

The Winters' equation, based on patient data, predicts the degree of the respiratory compensation (the decrease in PCO_2) in metabolic acidosis. As Equation 17–1 illustrates:

$$PCO_2 = [1.5 \times HCO_3^-] + 8 \pm 2$$

An alternative to the Winters' equation is the observation by Narins and Emmett that in compensated metabolic acidosis, the arterial PCO_2 is usually the same as the last two digits of the arterial pH. For example, a pH of 7.26 predicts a PCO_2 of 26 mm Hg.

Calculating the Anion Gap

The law of electroneutrality states that the net positive and negative charges of the serum must be equal. Because not all charged particles are measured, an anion gap exists, which is derived as shown in Equation 17–2:

$$\text{Anion gap} = (Na^+) - (Cl^- + HCO_3^-)$$

The normal anion gap is 7 ± 4 mEq/L. A variety of conditions result in a rise or fall of the anion gap. High anion gaps result from increased presence of unmeasured anions or decreased presence of unmeasured cations (Table 17–1). Similarly, a low anion gap results from an increase in unmeasured cations or a decrease in unmeasured anions (Table 17–2).

Metabolic Acidosis

When a metabolic acidosis is present, the serum anion gap should be analyzed. This determination should be made after correcting the anion gap for the effect of hypoalbuminemia, a common confounding factor. The anion gap decreases approximately 3 mEq/L per 1 g/dL decrease in the serum albumin. A high-anion-gap metabolic acidosis results from the absorption or generation of an acid that dissociates into an anion other than Cl^- that is neither excreted nor metabolized. Normal-anion-gap metabolic acidosis results from the absorption or generation of an acid that dissociates into H^+ and Cl^-. Normal-anion-gap acidosis, also referred to as hyperchloremic metabolic acidosis, may be caused by intestinal or renal bicarbonate losses, as in diarrhea or renal tubular acidosis, respectively. Tables 17–3 and 17–4 list other causes of high- and normal-anion-gap metabolic acidoses.

Narrowing the Differential Diagnosis of a High-Anion-Gap Metabolic Acidosis

As always, the clinical history and physical examination may provide essential clues to the diagnosis. When these clues are absent, the laboratory analysis must be relied on, as follows:

1. *Begin with the electrolytes and glucose:* A rapid glucose reagent test should confirm or exclude the possibility of hyperglycemia and raise the

TABLE 17–1. Xenobiotic and Other Causes of a High Anion Gap

Increased unmeasured anions
Metabolic acidosis (see Table 17–3)
Dehydration
Therapy with sodium salts of unmeasured anions
Sodium citrate
Sodium lactate
Sodium acetate
Therapy with certain antibiotics
Carbenicillin
Sodium penicillin
Alkalosis
Decrease in unmeasured cations
Simultaneous hypomagnesemia, hypocalcemia, and hypokalemia

TABLE 17–2. Xenobiotic and Other Causes of a Low Anion Gap

Increase in unmeasured cations
Hypercalcemia
Hypermagnesemia
Hyperkalemia
Lithium poisoning
Multiple myeloma
Decrease in unmeasured anions
Hypoalbuminemia
Dilution
Overestimation of the chloride
Bromism
Iodism
Nitrate excess

TABLE 17–3. Xenobiotic and Other Causes of a High-Anion-Gap Metabolic Acidosis

Carbon monoxide
Cyanide
Ethylene glycol
Hydrogen sulfide
Isoniazid
Iron
Ketoacidoses (diabetic, alcoholic, and starvation)
Lactate
Metformin
Methanol
Paraldehyde
Phenformin
Salicylates
Sulfur (inorganic)
Theophylline
Toluene
Uremia (acute or chronic renal failure)

Note: Many clinicians rely on the mnemonic **MUDPILES** to help remember this differential diagnosis where M represents methanol; U, uremia; D, diabetic ketoacidosis; P, paraldehyde; I, iron; L, lactic acidosis; E, ethylene glycol; and S, salicylates.

TABLE 17–4. Xenobiotic Causes of a Normal-Anion-Gap Metabolic Acidosis

Acetazolamide
Acidifying agents
Ammonium chloride
Arginine hydrochloride
Hydrochloric acid
Lysine hydrochloride
Cholestyramine
Sulfamylon
Toluene
Topiramate

possibility of diabetic ketoacidosis. An elevated BUN and creatinine are essential to diagnose acute or chronic renal failure.

2. *Proceed to the urinalysis:* A dipstick for glucose and ketones helps with the diagnosis of diabetic ketoacidosis and other ketoacidoses. However, the absence of urinary ketones does not exclude a diagnosis of alcoholic ketoacidosis and ketones are often present in severe salicylism. Also, calcium oxalate crystals may be present in the urine of an ethylene glycol–poisoned patient. Finally, a urine ferric chloride test, which is highly sensitive and specific for the presence of salicylates, should be performed.
3. An arterial or venous blood lactate concentration can be helpful. In theory, if the lactate (measured in mEq/L) can entirely account for the fall in serum [HCO_3^-], then the cause of the increased anion gap can be attributed to lactic acidosis. However, glycolate (a metabolite of ethylene glycol) can produce a significant false-positive elevation of lactate.

When the above analysis is not productive, the diagnosis is usually toxic alcohol ingestion, starvation, alcoholic ketoacidosis (with minimal urine ketones), or a multifactorial process involving small amounts of lactate and other anions. One approach is to provide the patient with 1–2 hours of intravenous hydration, dextrose, and thiamine. If the acidosis improves, the etiology is either ketoacidosis or lactic acidosis.

The Osmol Gap

The osmol gap is defined as the difference between the values for the measured osmolality and the calculated osmolarity. One of the most common equations for the osmol gap is Equation 17–3:

$$2(Na^+ \text{in mEq/L}) + (\text{glucose in mg/dL})/18 + (\text{BUN in mg/dL})/2.8$$

where normal values are 2 ± 6 mOsm. There are many limitations to the osmol gap calculation. As a result, small or even negative osmol gaps can never be used to exclude toxic alcohol ingestion. Also, although large osmol gaps may be suggestive of toxic alcohol ingestions, common conditions, such as alcoholic ketoacidosis, lactic acidosis, renal failure, and shock, are all associated with elevated osmol gaps. However, in the presence of very high osmol gaps (>50–70 mOsm), the diagnosis of toxic alcohol ingestion is usually confirmed.

Differential Diagnosis of a Normal-Anion-Gap Metabolic Acidosis

Although the differential diagnosis for a normal-anion-gap metabolic acidosis is extensive (Table 17–4), most cases result from either urinary or gastrointestinal HCO_3^- losses: renal tubular acidosis (RTA) or diarrhea, respectively. A urinary anion gap is suggested may help narrow the differential diagnosis (Equation 17–4):

$$(NA^+ + K^+) - (Cl^-)$$

The size of this gap is inversely correlated with urinary ammonium (NH_4^+) excretion. As NH_4^+ elimination increases, the urinary anion gap narrows and may become negative, because NH_4^+ serves as an unmeasured urinary cation and is accompanied predominantly by Cl^-.

The urinary anion gap in usually negative (–20 ± 5.7 mEq/L) in patients with diarrhea, as compared to positive (23 ± 4.1 mEq/L) in those with RTA.

Management Principles in Patients with Metabolic Acidosis

The treatment of metabolic acidosis depends on its severity and cause. In most cases of severe poisoning, a serum [HCO_3^-] of less than 8 mEq/L and arterial pH values of less than 7.20 should probably be treated with HCO_3^- to increase the pH above 7.20. In patients with arterial pH values greater than 7.20, the cause of the acidosis should guide therapy. Metabolic acidosis primarily caused by the overproduction of acid (eg, ketoacidosis, lactic acidosis, diarrhea), will require very large quantities of HCO_3^- and may not respond well to HCO_3^- therapy. Treatment in these patients should be directed at the cause of acidosis (eg, insulin in diabetic ketoacidosis; fomepizole in methanol and ethylene glycol poisonings). Metabolic acidosis primarily caused by underexcretion of acid (eg, acute or chronic renal failure, RTA), should be treated with a low-protein diet (if feasible) and oral $NaHCO_3$ or substances that generate HCO_3^- during metabolism.

METABOLIC ALKALOSIS

Adverse Effects of Metabolic Alkalosis

Life-threatening metabolic alkalosis is rare but can result in tetany (from decreased ionized [Ca^{2+}]), weakness (from decreased serum [K^+]), altered mental status leading to coma, seizures, and cardiac dysrhythmias. In addition, metabolic alkalosis shifts the oxyhemoglobin dissociation curve to the left, impairing tissue oxygenation. Respiratory compensation is irregular and inadequate at best; consequently, hypoxia is more undesirable than alkalemia.

Approach to the Patient with Metabolic Alkalosis

Metabolic alkalosis results from gastrointestinal or urinary loss of acid, administration of exogenous base, and/or renal HCO_3^- retention (ie, impaired renal HCO_3^- excretion). Table 17–5 lists the causes of metabolic alkalosis.

The etiologies of metabolic alkalosis can be characterized from a therapeutic standpoint as Cl^--responsive or Cl^--resistant. Chloride-responsive etiologies such as diuretic use, vomiting, and nasogastric suction, or Cl^- diarrhea, are usually associated with a low urinary [Cl^-] (<10 mEq/L). These disorders respond rapidly to infusion of 0.9% NaCl solution. Chloride-resistant disorders are characterized by urinary [Cl^-] greater than 10 mEq/L and tend to be resistant to 0.9% NaCl solution therapy. These disorders often require K^+ repletion or agents that reduce mineralocorticoid effects, such as spironolactone, before correction can occur.

XENOBIOTIC-INDUCED ALTERATIONS OF WATER BALANCE

The diagnosis and treatment of abnormal serum electrolyte concentrations are usually addressed after repletion of the ECFV deficit with isotonic, Na^+-containing fluids (eg, blood products, 0.9% NaCl solution, lactated Ringer solution). Abnormalities of body water balance manifest as hypernatremia and hyponatremia, and specifically on the toxicologically relevant syndromes of diabetes insipidus (DI) and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Both serum [Na^+] and plasma osmolality vary inversely with changes in the quantity of body water. Changes in osmolality are caused by changes in water intake and insensible (dermal, respiratory, and stool) and sensible (urinary, sweat)

TABLE 17–5. Xenobiotic and Other Causes of Metabolic Alkalosis

Gastrointestinal acid loss
Nasogastric suction (protracted)
Vomiting (protracted)
Urinary acid loss
Common
Diuretics
Glucocorticoids
Rare
Hypercalcemia
Licorice (glycyrrhizic acid)
Magnesium deficiency
Base administration
Acetate (dialysis or hyperalimentation)
Bicarbonate
Carbonate (antacids)
Citrate (posttransfusion)
Milk alkali syndrome
Renal bicarbonate retention
Hypercapnia (chronic)
Hypochloremia
Hypokalemia
Volume contraction

water losses. Urinary water losses are controlled by the hormone arginine vasopressin (antidiuretic hormone [ADH]). Increases in the osmolality stimulate ADH synthesis and release. Antidiuretic hormone increases the water permeability of the distal convoluted tubule and collecting duct, increasing water reabsorption and urine concentration, and minimizing urinary water losses.

Hypernatremia

Table 17–6 lists xenobiotics that cause hypernatremia.

Diagnosis and Treatment

The symptoms of significant hypernatremia consist largely of altered mental status ranging from confusion to coma and neuromuscular weakness, occasionally resulting in respiratory paralysis. If hypernatremia is associated with Na^+ losses and marked ECFV depletion, cardiovascular symptoms, tachycardia, and orthostatic hypotension may be present. Treatment consists of replacing the Na^+ deficit first, if necessary (with isotonic fluids such as 0.9% NaCl solution), and then the water deficit. The water deficit may be estimated by assuming that the fractional increase in serum [Na^+] is equal to the fractional decrease in total body water. Thus, a serum [Na^+] that has increased by 10% (from 144 mEq/L to 158 mEq/L) indicates that the water deficit is 10% (3.6 L in a 60-kg person with 36 L of body water).

When the hypernatremia develops over several hours, rapid correction is indicated. However, when hypernatremia develops over several days, or when the duration is unknown, slow correction of hypernatremia (over several days) is recommended. The adaptation of brain cells to the water deficit (including the

TABLE 17–6. Xenobiotic Causes of Hypernatremia

Sodium gain
Antacids (baking soda)
Sodium salts (bicarbonate, chloride, citrate, hypochlorite)
Seawater
Water loss
Cholestyramine
Diuretics
Glycerol
Lactulose
Mannitol
Povidone-iodine
Sorbitol
Urea
Water loss: Diabetes Insipidus
α-Adrenergic antagonists
Amphotericin
Colchicine
Demeclocycline
Ethanol
Foscarnet
Glufosinate
Lithium
Lobenzarit disodium
Methoxyflurane
Mesalazine
Minocycline
Opioid antagonists
Propoxyphene
Rifampin
Streptozotocin
Vasopressin V_2-receptor antagonists

loss of intracellular solute) makes cerebral edema a frequent result of rapid water replacement.

Diabetes Insipidus

The greatest water losses and most severe cases of hypernatremia occur during DI, which is always characterized by hypotonic polyuria. Diabetes insipidus may be neurogenic (resulting from failure to sense a rising osmolality, or from a failure to release ADH) or nephrogenic (resulting from failure of the kidney to respond appropriately to ADH) (Table 17–6).

Diagnosis

Urine volumes typically exceed 30 mL/kg/d and may be as high as 9 L/d with nephrogenic DI and 12–14 L/d with neurogenic (central) DI. Neurogenic DI resulting from hypothalamic or pituitary damage is typically associated with other signs of neuroendocrine dysfunction. The diagnosis of DI is established by the occurrence of dilute urine (urine osmolality <300 mOsm/kg, urine specific gravity <1.010) in the presence of increased serum $[Na^+]$, and serum osmolality greater than 295 mOsm/kg. A trial of desmopressin (DDAVP), an arginine vasopressin analog, helps to differentiate between neurogenic and nephrogenic DI. In neurogenic

DI, the patient promptly responds to DDAVP with a decrease in urine output and increase in urine osmolality. In nephrogenic DI, DDAVP has no significant effect.

Treatment

The initial approach to the hypernatremic patient with DI involves the repletion of the water deficit (as described above) and the restoration of electrolyte balance, if necessary. If a reversible cause for the DI can be established, it should be corrected. Patients with nephrogenic DI can be treated with thiazide diuretics, prostaglandin inhibitors, and/or amiloride.

Hyponatremia

Hyponatremia may be associated with a high, normal, or low plasma osmolality. Hyperglycemic causes hyponatremia because the increase in plasma osmolality caused by glucose shifts water from the intracellular to the extracellular space. The reduction in serum [Na^+], which may cause symptoms, is approximately 2 mEq/L per 100 mg/dL increase in serum glucose concentration. Almost all other causes of hyponatremia are associated with a low plasma osmolality.

Hyponatremia associated with a low plasma osmolality usually results from water intake in excess of the renal capacity to excrete it. Xenobiotic-induced water excess comparable to psychogenic polydipsia is quite uncommon. An example occurs during urologic procedures, such as transurethral resection of the prostate (TURP), where large volumes of irrigation solution are required. TURP is performed with glycine-containing irrigation solutions. When 1.5% glycine (osmolality 220 mOsm/Kg) is absorbed through the prostatic venous plexus, a rapid reduction in serum [Na^+] results and will persist until the glycine is metabolized. Symptoms are probably a result of hyponatremia, the glycine itself, and NH_3, a glycine metabolite. A similar complication is also described during hysteroscopy.

Most cases of hyponatremia are caused by water intake in excess of a reduced renal excretory capacity. This reduction in urinary water excretion may be physiologic (as during ECF sodium depletion) or pathologic (in association with renal failure, heart failure, or cirrhosis of the liver). Because these conditions are accompanied by alterations in renal sodium handling, signs and symptoms of ECFV depletion (eg, postural hypotension) or excess (eg, edema), respectively, usually accompany the hyponatremia. Other patients cannot excrete water normally because malignancy or various brain or pulmonary diseases cause ADH secretion. Patients with excess secretion and/or action of ADH, who have near-normal ECFV, are said to have the SIADH. Table 17–7 summarizes these and other causes of hyponatremia.

SIADH

SIADH is characterized by hyponatremia and plasma hypotonicity in the absence of abnormalities of ECFV, adrenal, thyroid, or renal function. There are many nontoxicologic etiologies of SIADH, most of which involve pulmonary or intracranial processes. These causes include infections, malignancies, and surgery. Table 17–7 summarizes xenobiotics that produce SIADH.

Diagnosis

The clinical presentation of patients with hyponatremia depends on the cause, the absolute serum [Na^+], and the rate of decline in serum [Na^+]. Patients with associated ECFV excess or depletion present with evidence of altered ECFV, as well as signs and symptoms of the disease that caused the abnormality in ECFV, such as adrenal insufficiency or heart failure. Patients with hyponatremia and a low

TABLE 17–7. Xenobiotic and Other Causes of Hyponatremia

Arginine
Captopril and other angiotensin-converting enzyme inhibitors
Diuretics
Glycine (transurethral prostatectomy syndrome)
Lithium
Nonsteroidal antiinflammatory drugs
Primary polydipsia
Silver nitrate
SIADH
Amiloride
Amitriptyline (and other tricyclic antidepressants)
Biguanides
Carbamazepine (and oxcarbamazepine)
Cisplatin
Clofibrate
Cyclophosphamide
Desmopressin (DDAVP)
Diazoxide
Indapamide
Indomethacin
MDMA (methylenedioxymethamphetamine)
Metformin
Nicotine
Opioids
Oxytocin
Selective serotonin reuptake inhibitors
Sulfonylureas
Thioridazine
Tranylcypromine
Vasopressin
Vincristine and vinblastine

plasma osmolality (excluding those with primary polydipsia) all have a urinary osmolality that is relatively high, regardless of whether they have excess, diminished, or normal ECFV. Consequently, these disorders can only be differentiated by the history, physical examination, and other laboratory tests.

Chronic, slow depression of the serum [Na^+] is usually well tolerated, whereas rapid decreases may be associated with symptoms and sometimes catastrophic events. Symptoms include headache, nausea, vomiting, restlessness, disorientation, depression, apathy, irritability, lethargy, weakness, and muscle cramps. In more severe cases, respiratory depression, coma, and seizures develop.

The diagnosis of SIADH is based on hyponatremia, a low plasma osmolality, and impaired urinary dilution in the absence of edema, hypotension, hypovolemia, and renal, adrenal, or thyroid dysfunction. A serum uric acid concentration may be helpful in differentiating SIADH from other causes of hyponatremia. Patients with SIADH have hypouricemia, whereas patients exhibiting ECFV excess or depletion characteristically have hyperuricemia.

Treatment

Treatment of patients with demonstrable ECFV excess or depletion should be directed at the abnormal ECFV and its cause, rather than at the hyponatremia. In patients with SIADH, treatment begins with fluid restriction.

In all asymptomatic or mildly symptomatic patients (usually patients with chronic hyponatremia of more than 2 days duration), correction should proceed slowly, and certainly at a rate less than 0.5 mEq/L per hour during the first 24 hours. This is because too rapid correction of hyponatremia may increase the risk central pontine myelinolysis. *Water restriction is usually sufficient, but occasionally demeclocycline may be appropriate*.

When hyponatremia is associated with life-threatening clinical presentations, careful infusion of hypertonic (3%) saline (eg, 0.5–1 mL/kg/h) with or without furosemide is indicated. The goal is to increase the serum [Na^+] by 1–2 mEq/L/h, or 10%, over 12–24 hours, or until the symptoms abate. Equation 17–5 might be helpful for calculating the rate of correction of hyponatremia.

When one liter of fluid is infused:

$$\text{The change in the serum } Na^+ = \frac{\text{infusate } Na^+ - \text{serum } Na^+}{\text{total body water} + 1 \text{ liter}}$$

Where infusate Na^+ concentrations in mEq/L equal:

3% sodium chloride	513
0.9% sodium chloride	154
Lactated Ringer solution	130
0.45% sodium chloride	77
0.33% sodium chloride	51

XENOBIOTIC-INDUCED ELECTROLYTE ABNORMALITIES

Potassium

Xenobiotic-induced alterations in serum [K^+] are potentially more serious than alterations in other electrolytes because of potassium's critical role in a variety of homeostatic processes. The total body potassium content of an average adult is about 54 mEq/kg, of which only 2% is located in the intravascular space. The relationship between total body stores and serum [K^+] is not linear, and small changes in the total body potassium may result in dramatic alterations in serum concentrations, and, more importantly, in the ratio of extracellular to intracellular [K^+].

The body has two major defenses against a potassium load: acutely, potassium is transferred into cells; chronically, potassium is excreted in the urine. Table 17–8 lists xenobiotics commonly associated with hypo- and hyperkalemia.

Patients with hypokalemia are often asymptomatic when the decrease in serum [K^+] is mild (serum concentrations of 3.0–3.5 mEq/L). Occasionally, hypokalemia interferes with renal concentrating mechanisms and polyuria is noted. More significant potassium deficits (serum concentrations of 2.0–3.0 mEq/L) cause generalized malaise and weakness. As the [K^+] levels fall to less than 2 mEq/L, weakness becomes prominent and areflexic paralysis and respiratory failure can occur, often necessitating intubation and mechanical ventilation. Common ECG findings of hypokalemia include depression of the ST segment, decreased T-wave amplitude, and increased U-wave amplitude. These findings may herald life-threatening rhythm disturbances.

Treatment of hypokalemia involves discontinuing or removing the offending agent and correcting the potassium deficit. Potassium supplementation may be given orally and/or intravenously.

In life-threatening conditions with intensive care monitoring, intravenous administrations of 20 mEq/h are well-tolerated. In adults, each 20 mEq of potassium results in an average increase in serum [K^+] of 0.25 mEq/L.

After oral overdoses of potassium salts, patients usually complain of nausea and vomiting. Ileus, and intestinal irritation, bleeding, and perforation may com-

TABLE 17–8. Xenobiotic Causes of Altered Serum Potassium

Hypokalemia	Hyperkalemia
Aminoglycosides	Amiloride
Amphotericin	Angiotensin-converting enzyme inhibitors
Barium (soluble salts)	Angiotensin receptor blockers
β-Adrenergic agonists	α-Adrenergic agonists (phenylephrine)
Bicarbonate	β-Adrenergic antagonists
Caffeine	Arginine hydrochloride
Carbonic anhydrase inhibitors	Cardioactive steroids
Cathartics	Fluoride
Chloroquine	Heparin
Cisplatin	Nonsteroidal antiinflammatory drugs
Dextrose	Penicillin (potassium)
Hydroxychloroquine	Potassium salts
Insulin	Spironolactone
Licorice (glycyrrhizic acid)	Succinylcholine
Loop diuretics	Triamterene
Metabolic alkalosis	Trimethoprim
Oral hypoglycemics	
Osmotic diuretics	
Quinine	
Salicylates	
Sodium penicillin and its analogs	
Sodium polystyrene sulfate	
Sympathomimetics	
Theophylline	
Thiazide diuretics	
Toluene	

plicate the clinical course. In the absence of potassium ingestion, gastrointestinal symptoms of hyperkalemia are usually very mild. Neuromuscular manifestations include weakness with an ascending flaccid paralysis and respiratory compromise, with intact sensation and cognition. The cardiac manifestations of hyperkalemia are distinct, prominent, and life-threatening. Although the progression of ECG changes is very reproducible, there is tremendous individual variation with respect to the serum [K^+] at which these ECG findings occur. Initially, the only ECG finding may be the presence of tall, peaked T waves. As the serum [K^+] increases, the QRS complex tends to blend into the T waves, the P-wave amplitude decreases, and the PR interval becomes prolonged. Next, the P wave is lost and ST-segment depression occurs. Finally, the distinction between the S and T waves becomes blurred and the ECG takes on a sine wave configuration. Hemodynamic instability and cardiac arrest can result.

The treatment of severe hyperkalemia includes standard airway management, methods to reverse the ECG effects, methods to transfer K^+ to the intracellular space, and methods to enhance K^+ elimination. Calcium (eg, $CaCl_2$ 10–20 mEq administered intravenously) works almost immediately to protect the myocardium against the effects of hyperkalemia, although it does not reduce the serum [K^+]. However, a potentially life-threatening interaction occurs when the patient with cardioactive steroid toxicity is given Ca^{2+}; thus, this therapeutic modality is relatively contraindicated in such circumstances. The administration of insulin (and dextrose to prevent hypoglycemia), $NaHCO_3$, and/or inhalation of a β-adrenergic agonist all stimulate potassium entry into cells. Cationic exchange resins, such as Na^+ polystyrene sulfonate, take somewhat longer (about 45 minutes), but

they enhance gastrointestinal potassium loss. Hemodialysis or peritoneal dialysis may be useful, especially when significant renal impairment is present.

Calcium

Calcium is the most abundant mineral in the body and 98–99% is located in bone. Approximately half of the remaining 1–2% of the body's calcium is bound to plasma proteins (mostly albumin), and most of the rest is complexed to various anions, with free, ionized calcium representing a very small fraction of extraosseous stores. The serum [Ca^{2+}] is maintained through interactions between dietary intake and renal elimination, modulated by vitamin D activity, parathyroid hormone, and calcitonin. Table 17–9 lists causes of hypo- and hypercalcemia.

Symptoms of hypercalcemia consist of lethargy, muscle weakness, nausea, vomiting, and constipation. Life-threatening manifestations include complications from altered mental status such as aspiration pneumonia and cardiac dysrhythmias. Treatment of clinically significant hypercalcemia focuses on decreasing gastrointestinal absorption, increasing distribution into bone, and enhancing renal excretion through forced diuresis with intravenous 0.9% NaCl solution and furosemide. Hemodialysis may be required when significant renal impairment is present.

Symptoms of hypocalcemia consist largely of neuromuscular findings, including paresthesia, cramps, carpopedal spasm, tetany, and seizures. Although ECG abnormalities are common, life-threatening dysrhythmias are rare. Treatment strategies focus on calcium replacement. When hypomagnesemia or hyperphosphatemia is present, these abnormalities should be corrected or calcium replacement may fail.

Magnesium

Magnesium is the fourth most abundant cation in the body (after Ca^{2+}, Na^{+}, and K^{+}), with a normal total body store of about 2000 mEq in a 70-kg human. Approximately 50% of magnesium is stored in bone, with most of the remainder distributed in the soft tissues. Only approximately 1–2% of magnesium is located in the extracellular fluid; consequently, serum levels correlate poorly with total

TABLE 17–9. Xenobiotic Causes of Altered Serum Calcium

Hypocalcemia	Hypercalcemia
Aminoglycosides	Aluminum
Bicarbonate	Androgens
Bisphosphonates	Antacids (calcium-containing)
Calcitonin	Antacids (magnesium-containing)
Citrate	Cholecalciferol and other vitamin D analogs
Ethanol	Glucocorticoids
Ethylene glycol	Lithium
Fluoride	Milk–alkali syndrome
Furosemide	Tamoxifen
Mithramycin	Thiazide diuretics
Neomycin	Vitamin A
Phenobarbital	
Phenytoin	
Phosphate	
Theophylline	
Valproate	

TABLE 17–10. Xenobiotic Causes of Altered Serum Magnesium

Hypomagnesemia	Hypermagnesemia
Aminoglycosides	Antacids (magnesium-containing)
Amphotericin	Cathartics (magnesium-containing)
Cisplatin	Lithium
Citrate	Magnesium sulfate
Cyclosporine	
DDT	
Ethanol	
Fluoride	
Foscarnet	
Insulin	
Laxatives	
Loop diuretics	
Methylxanthines	
Osmotic diuretics	
Phosphates	
Strychnine	
Thiazide diuretics	

body stores. Magnesium homeostasis is maintained through dietary intake, and renal and gastrointestinal losses, modulated by hormonal effects. Table 17–10 lists the causes of hyper- and hypomagnesemia.

The symptoms of hypermagnesemia correlate roughly with serum concentrations. At serum [Mg^{2+}] of about 3–10 mEq/L, patients feel weak, nauseated, flushed, and thirsty. Bradycardia, a widened QRS complex on ECG, hypotension, and decreased deep tendon reflexes may be noted. As levels increase, hypoventilation, muscle paralysis, and ventricular dysrhythmias occur. Serum [Mg^{2+}] greater than 10 mEq/L, and especially those greater than 15 mEq/L, often cause death.

When significant neuromuscular or ECG manifestations are noted, administration of $CaCl_2$ 5–20 mEq intravenously will reverse some of the toxicity. Further therapy should focus on enhancing renal excretion by administering fluids and loop diuretics such as furosemide. In the presence of renal failure or inadequate renal excretion, hemodialysis will rapidly correct hypermagnesemia.

The symptoms of hypomagnesemia are lethargy, weakness, fatigue, neuromuscular excitation (tremor and hyperreflexia), nausea, and vomiting. Dysrhythmias may occur, especially during therapy with cardioactive steroids. Signs and symptoms consistent with hypocalcemia and hypokalemia also may be present. Although either oral or parenteral supplementation is usually acceptable for mild hypomagnesemia, parenteral therapy is required when significant clinical effects are present. When oral therapy is indicated, a normal diet, or magnesium oxide, magnesium chloride, or magnesium lactate in divided doses (20–100 mEq of magnesium daily) often corrects the hypomagnesemia. When hypomagnesemia is severe or symptomatic, several authors suggest that in the absence of renal insufficiency, the administration of magnesium sulfate 16 mEq (2 g) intravenously over several minutes to a maximum of 1 mEq/kg of magnesium in a 24-hour period. During any substantial magnesium infusion, frequent serum [Mg^{2+}] determinations should be obtained and the presence of reflexes documented. If hyporeflexia occurs, the magnesium infusion should be discontinued.

18 Psychiatric Principles

Psychiatric problems may be the cause or the effect of many toxicologic presentations. Suicide attempts and aggressive behaviors are commonly associated with intoxications and can be uniquely difficult to assess and manage. The signs and symptoms displayed by these patients are sometimes considered to be totally voluntary and deliberate and at other times totally "out of control" and irrational. The truth is usually more complex.

SUICIDE AND SELF-INJURIOUS BEHAVIOR

Suicide and self-injurious behavior are among the most common and challenging emergency department (ED) presentations. Each year there are an estimated 790,000 suicide attempts in United States, including more than 30,000 actual suicides. Suicide is the 11th leading cause of death in America and third leading killer of young people. In 2002, more than 124,000 visits to US ED were made after attempted suicides or other self-harm incidents among persons between 10 and 24 years of age. Women are three times more likely than men to attempt suicide and often use poison in their attempts.

The etiologies of suicidal crises are heterogeneous, with suicide the final outcome of many possible psychiatric conditions and social circumstances. Suicidal ideation may be deliberately concealed, making it critical for healthcare providers to address this possibility with all patients as part of their medical history. Early identification of the acutely suicidal patient is difficult but important for emergency physicians to detect in order to effectively intervene and prevent death.

It is difficult for the physician to assess the patient's intention for self-injurious behavior. Self-injurious behavior may be caused by factors other than suicidal intent. Intentional self-poisoning or "overdosing," for example, is a common method of attempting suicide, but intentional overdoses must also be differentiated from unintentional, particularly in the young and the developmentally challenged, as well as those with dementia and those who chronically abuse drugs. In addition, self-injurious behavior may be the result of a patient's attempt to manipulate others or their environment, to cope with emotional lability, or as a reaction to delusions or hallucinations.

The tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) remain among the most common drugs implicated in suicide because of their toxicity and frequent use in the populations at risk. However, a decline in self-poisoning from this class of medications may be related to their decreased use since the selective serotonin reuptake inhibitors (SSRIs) became available.

PSYCHIATRIC MANAGEMENT OF SELF-POISONING

Focused Psychiatric Assessment

At a relatively early point in the patient's course, when the patient is lucid, a focused psychiatric assessment is critical to address specific clinical concerns. A thorough psychiatric consultation is warranted once the patient is

medically stable. The determination that the patient is stable is not solely established on the basis of blood concentrations of a xenobiotic or ancillary medical tests, but rather when the emergency physician or medical toxicologist with an understanding of pharmacokinetics deems it appropriate. Psychiatric examination is warranted when the altered mental status has cleared.

A focused assessment is necessary to ascertain elopement risk or decisional capacity. A high level of supervision should be maintained, and a patient should not be allowed to leave until an adequate assessment of the individual's mental status is completed.

In general, patients are presumed competent and must consent to treatment, but the issue of decisional capacity frequently arises. Patients may request their discharge, refuse care, or become aggressive. Aggression may arise from lingering effects of a toxic ingestion, severe anxiety, fear, anger at the loss of autonomy, or the discomfort of unpleasant procedures. Although patients may respond to verbal limit setting and repeated explanations of their care, they may also require pharmacologic or physical restraint and involuntary treatment. Patients are not allowed to make poor healthcare decisions if their ability to weigh the risks and benefits of the proposed care is limited by cognitive deficits or mental illness. In the setting of intoxication, appropriate care may be provided under the doctrine of implied consent.

The emergency exception to the doctrine of informed consent may also apply in circumstances where self-injury is suspected. The emergency exception permits forcible detention, restraint, medication over objection, and necessary medical care until psychiatric assessment can be accomplished. After the management of the immediate medical emergency and resolution of intoxication, suspected self-injury is sufficient evidence of impaired decisional capacity for the emergency physician to hold a patient for further psychiatric assessment. The emergency physician should note the patient's objections in the patient's medical record and indicate the basis for the determination of diminished capacity.

After the patient is stabilized, there may be a need for a more thorough assessment of decisional capacity. Psychiatric consultation is appropriate at this stage to help document the degree of impairment, determine the etiology, and predict the likely course.

Immediate Risk

After safety considerations have been addressed, the aim of the focused psychiatric assessment moves toward a determination of immediate suicide risk.

Reliability and Confidentiality

Evasiveness, lack of detail, inconsistency, and improbability may lead to an unreliable history. It is appropriate to question the patient again about the implausible aspects of the history and offer an opportunity for the patient to recount questionable events and details. This is often successful, although revised accounts may, of course, also be suspect. The most important step from the standpoint of both clinical care and risk management is to locate other sources of information to clarify or verify the patient's situation and account of events. A careful review of all previous medical and psychiatric records is critical.

Comprehensive Psychiatric Assessment

The comprehensive psychiatric assessment includes a characterization of current and past suicidal ideation, an exploration of "risk factors," and a formu-

lation of a diagnostic impression. These three elements help to determine attendant risks and guide treatment planning.

Stress Vulnerability Model

The best understanding of suicide at this time is that it results from intrinsic vulnerability factors interacting with extrinsic circumstances. Intrinsic vulnerability may be the result of a variety of traits such as impulsivity or conditions such as depression, anxiety, and hopelessness. Extrinsic factors include stressful life events, access to lethal means, and a host of other factors, positive and negative.

Characterization of Suicidal Ideation

The core of the suicide risk assessment is a detailed discussion of the patient's suicidal thoughts and urges. This must be included in every mental status examination. The clinician may spend a few moments talking with the patient about the point in life when he or she was most disheartened. Ultimately, all patients must be asked directly if they ever felt like "killing" themselves (active suicidal ideation). Suicidal feelings range from a relatively inchoate wish to die, perhaps from a fatal disease or injury, and then proceed to consideration of various active means of hastening death. Other dimensions to assess include frequency, urgency, chronicity, reactivity to positive and negative external events, and subjective distress (Table 18–1).

Psychiatric Illness and Suicide

One major consideration in suicide risk assessment is the occurrence of severe mental illness. Suicide risk for individuals with severe mental illness is 20–40 times higher than the risk for the general population.

TABLE 18–1. Characterization of Suicidal Ideation

Dimension	Benign	Intermediate	Malignant
Onset	None, acute	Chronic, stable	New or fluctuating
Frequency	Occasional	Daily	Constant
Persistence	Fleeting thoughts	Persistent thoughts	Preoccupation
Urgency	Disinterested	Engaged	Intense
Complexity	Simple	Some detail	Elaborate
Activity	Passive ideas	Plans without action	Action
Emotional response	Death repellent	Ambivalent	Death desirable
Circumstances	Victim identifies one clear precipitant	Several complex contributory stressors	Either noncontributory or overwhelming stressors
Alternatives	Some, realistic	Few, problematic	Seems hopeless
Insight	Recognizes remediable psychological problem	Overvalued ideas present, temporarily reassured	Morbid delusions present, reassurance impossible
Intent	Opposed to suicide	Suicide acceptable but prefers to live	Resolutely suicidal

Demographic Risk Factors

Although not specifically predictive, suicide is statistically more common in men than in women, and in whites than in nonwhites. Younger black men, however, have approximately the same suicide rate as white men of the same age. Suicide rates for both black and white adolescents (15–19 years of age) have been increasing. In contrast, suicide rates in the elderly have decreased threefold since 1940, but suicide in the elderly still occurs in disproportionately high numbers. Any previous suicide attempt is an obvious risk factor, but medically serious attempts may be a more significant marker of risk.

Treatment

Following a comprehensive psychiatric assessment, the next step is to decide on treatment alternatives. Any patient who has made a suicide attempt must be considered to be at risk, and in such cases some further intervention is warranted. The risk of a subsequent lethal attempt is approximately 1% per year over the first 10 years. The risk is highest in the first month to 1 year after an attempt.

Some medications may be effective immediately for the treatment of severe anxiety or psychosis; however, in the case of depression, antidepressants require weeks of prescribed use to achieve a therapeutic effect, so they have no therapeutic role in ED management. In fact, it may be very dangerous to prescribe medications that are potentially lethal in overdose, such as the cyclic antidepressants or the nonselective monoamine oxidase inhibitors, to a person who has recently attempted suicide. The newer antidepressants, particularly the SSRIs, can be used safely as first-line drugs for treatment of most depression, because they are both effective in time and relatively safe in overdose. Initiation of any antidepressant therapy by a nonpsychiatric physician to a patient immediately after a suicide attempt is not recommended unless a tight linkage can be made between discharge and immediate (within days) aftercare by a community outreach team, a crisis clinic, or a psychiatrist.

After the patient's immediate symptoms have been treated in the ED, the next treatment decision is to determine the setting in which further treatment may safely be provided. Not all patients with suicidal ideation or even significant attempts necessarily require hospitalization, and there is still a substantial stigma attached to psychiatric hospitalization. In general, it should be the treatment used if less restrictive measures cannot ensure the patient's safety. If significant doubt exists about the safety of outpatient treatment, the patient should be held in the ED for further evaluation, admitted to a general hospital with close nursing supervision, or admitted to an acute care psychiatric unit.

The choice of inpatient or outpatient setting will depend on the balance of strengths and weaknesses of the patient, the involvement and competence of family or friends, the availability of a therapist in the community, and the ongoing stresses in the patient's life. Ideally, this decision should be made by a psychiatrist. Because a psychiatrist will not always be present in many facilities a trained mental health professional, such as a psychiatric social worker, a nurse clinician, or a psychologist, should be on call to every ED. When none of these providers are available, the patient should be detained in the ED until a practitioner with specific competence is available, or the patient can be transferred to another facility for evaluation. Laws provide for the involuntary commitment of the mentally ill under circumstances that vary from state to

state. Any acute, deliberate, self-injurious behavior generally qualifies. The practitioner should be familiar with the criteria for commitment and the classes of healthcare providers empowered under state law to mandate such commitment as well as provide crisis intervention.

Crisis intervention is a brief, highly focused form of therapy that seeks to deconstruct how a crisis occurred, with the intent of examining the patient's role. Often, patients have distorted perceptions of the crisis, and a gentle "correction" of catastrophic thinking can be extremely helpful.

Substance abuse treatment is ultimately an intermediate (weeks to months) to long-term (months to years) intervention. However, there are powerful initial steps that the emergency physician can take. Chief among these is confronting the patient about the medical consequences of substance use. Patients who are not subsequently admitted should be referred to outpatient programs such as Narcotics Anonymous, Cocaine Anonymous, and Alcoholics Anonymous.

VIOLENCE

Assessment

The comprehensive evaluation of the violent patient should include a complete physical examination. The examination may reveal the underlying cause of the violent behavior as well as ensuring the treatment of any secondary patient injuries. Laboratory analysis may include blood chemistries (thyroid-stimulating hormone [TSH]; glucose; electrolytes, including calcium, VDRL, RPR, B_{12}, and liver enzymes), a complete blood count, lumbar puncture, and neuroimaging as guided by the examination and clinical history.

Illicit xenobiotic and alcohol use often present with symptoms of violence. Acute intoxication with cocaine, amphetamines, or phencyclidine can produce extreme psychomotor agitation, delirium, and transient psychosis characterized by paranoia and hallucinations. Alcohol intoxication is characterized by typical signs of cerebellar dysfunction, such as slurred speech, ataxia, and incoordination; however, patients who are intoxicated are also at risk for violent behavior. Delirium can be a cause of aggression. Patients are often suddenly confused, frightened, or frankly psychotic as a result of impaired perception. Patients may require sedation or physical restraint to prevent injury to themselves and to staff. Although persons suffering from psychotic disorders are not generally aggressive, there are aspects of the psychotic state that place patients at risk for aggressive behavior. Paranoid ideation can serve to promote misperceptions of impending bodily harm ("They are trying to kill me"), sexual victimization ("Men and women are raping me"), and humiliation ("Everyone is laughing at me"). It follows that these fearful perceptions might provoke violent reactions in a patient.

Treatment

The acute pharmacotherapy of violent behavior is directed at reducing the level of arousal. Pharmacotherapy and seclusion or restraint are to be used only as long as needed to restore that relationship, for the benefit of the patient as well as other members of the milieu. The restoration of the treatment relationship is necessary to take measures to understand and address the cause of the agitation, with the input and consent of the patient, to prevent future incidents. As aggression derives from varied and multiple etiologies, it follows that there is much

debate about the specific psychotropic to be used, the route of administration, and the dosing interval. Studies examining the treatment of aggression and/or agitation have included such diverse populations as schizophrenics, acutely intoxicated patients (alcohol), trauma patients, postoperative patients, patients in alcohol withdrawal, and patients with presumed personality disorders. Treatment settings for these studies have included psychiatric inpatient units, intensive care units, and EDs. There are, however, specific clinical situations when benzodiazepines and antipsychotic agents might be preferentially used. Haloperidol has been safely used in the treatment of agitation and aggression in patients with psychoses, acute alcohol intoxication, and delirium. The drug can be administered orally, intravenously, or intramuscularly. Dosing intervals that range from 30 minutes to 2 hours, with a usual regimen of 5 mg haloperidol given every 30–60 minutes, result in most patients responding after 1–3 doses. The dose of haloperidol needed to achieve sedation rarely exceeds a total of 50 mg in acute management.

Benzodiazepines are also quite effective for sedation; their use has been examined in patients with psychoses, stimulant intoxication, sedative-hypnotic and alcohol withdrawal, and postoperative agitation. Lorazepam 1–2 mg can be given orally, intravenously, or intramuscularly and repeated at 30- or 60-minute intervals, respectively, until the patient is calm. Because diazepam is poorly absorbed from intramuscular sites, its route of administration is either intravenous or oral. Diazepam can be given as 5–10 mg IV with repeat dosing titrated to desired effect. Antipsychotics, particularly low-potency antipsychotics, are known to lower the seizure threshold in animals, so their use for patients with cocaine intoxication should be avoided. Studies examining the use of lorazepam and antipsychotic combinations in patients with psychiatric illness and delirium have found that these combinations relieved psychotic symptoms while allowing for a reduced dose of antipsychotic medications.

Physical Restraint

Isolating or restraining patients while observing them is also used in the treatment of violent behavior. Isolation or seclusion can help to diminish environmental stimuli, thereby reducing hyperreactivity, but this approach has limited applicability in a busy medical ED and is therefore not discussed in further detail here.

19 Neurologic Principles

DETERMINANTS OF NEUROTOXICITY

The clinical expression of neurotoxicity is related to many factors, including the chemical properties of the xenobiotic, the dose and route of administration, and xenobiotic interactions. Specific patient characteristics, such as age, gender, and comorbidities, are also important.

Chemical Properties of Xenobiotics

One of the most important determinants of neurotoxicity is the ability of a xenobiotic to penetrate the blood–brain barrier (BBB). Water-soluble molecules larger than M_r 200–400 (molecular weight ratio, or mass of a molecule relative to the mass of an atom) are unable to bypass the tight junctions. Xenobiotics with a high octanol-to-water partition coefficient are more likely to passively penetrate the capillary endothelium, and potentially the BBB, whereas those with a low partition coefficient may require energy-dependent facilitated transport.

Route of Administration

Although most xenobiotics gain access to the nervous system through the circulatory system, aerosolized solvents and heavy metals in industrial and occupational exposures gain CNS access through inhalation, traveling via olfactory and circulatory routes. Alternatively, some xenobiotics may move from the peripheral nervous system via retrograde axonal transport to the CNS.

Xenobiotic Interactions

Xenobiotic interactions can be pharmacokinetic (elevated blood concentration of a xenobiotic that overwhelms the BBB) or pharmacodynamic (acting on the same neuroreceptor with additive effects).

COMMON MECHANISMS OF NEUROTOXICITY

Alteration of Endogenous Neurotransmission

Xenobiotics can induce neurotoxicity by triggering changes in neurotransmission in either the central or peripheral nervous systems. In some cases, xenobiotics enhance neurotransmission through a specific receptor subtype (eg, cocaine), or, alternatively, synaptic neurotransmission may be impaired (eg, botulinum toxin).

Direct Receptor Interaction

Some xenobiotics are able to directly stimulate (eg, domoic acid at the AMPA [α-amino-3-hydroxy-5-methyl-4-isoxazole propionate] receptor) or inhibit (eg, antimuscarinic drugs at acetylcholine receptors).

Enzyme and Transporter Exploitation

Amphetamines are taken up by presynaptic neurons using existing catecholamine transporters. Once inside the cell, amphetamines induce the release of catecholamines stored in vesicles.

CLINICALLY RELEVANT XENOBIOTIC-MEDIATED CONDITIONS

Alterations in Consciousness

The toxicologic differential diagnosis of xenobiotics that induce alterations in mental status or consciousness is expansive. These xenobiotics can be broadly divided into those agents that produce some form of neuroexcitation and those that produce neuroinhibition. Xenobiotics resulting in neuroexcitation enhance neurotransmission of excitatory amino acids (EAA) or diminish inhibitory input from GABAergic neurons. The clinical presentation of the patient can vary, and some patients may be alert and confused, suffering from an agitated delirium or from hallucinations or a seizure.

Neuroinhibitory xenobiotics typically enhance γ-aminobutyric acid (GABA)-mediated neurotransmission, resulting in somnolence or coma. Benzodiazepines hyperpolarize cells by increasing inward movement of Cl^- ions through the chloride channel of the $GABA_A$ receptor. Clinical evaluation of patients with altered consciousness includes obtaining a complete history, including medications, comorbid conditions, occupation, and suicidal intent when relevant or available. Patients should have a complete physical examination, with particular attention to vital sign abnormalities or findings that may indicate a toxic syndrome. Assessment and correction of hypoxia or hypoglycemia should be performed. In some circumstances, an electrocardiogram may be useful (Chaps. 5 and 23).

Xenobiotic-Induced Seizures

Seizures are the most extreme form of neuroexcitation. Most seizures are short-lived and terminate spontaneously. Although variously defined, status epilepticus can involve 2 or more seizures without a lucid interval, or continuous seizure activity for longer than 15 minutes. Seizures may be caused by enhanced EAA neurotransmission (domoic acid, sympathomimetics), or by inhibition of GABAergic tone (isoniazid). Unlike patients with traumatic or idiopathic seizure disorders who have an identifiable seizure focus, the initiation and propagation of xenobiotic-induced seizures is diffuse. It is for this reason that non–sedative-hypnotic anticonvulsants, such as phenytoin, are ineffective in seizure termination.

Some clinical conditions appear to be centrally mediated tonic–clonic movements, but are caused by glycine inhibition in the spinal cord. Glycine is the major inhibitory neurotransmitter of motor neurons of the spinal cord. Glycine inhibition results in myoclonus, hyperreflexia, and opisthotonos, often without alteration in consciousness. Presynaptic glycine inhibition is caused by tetanospasmin (from *Clostridium tetani*), whereas postsynaptic glycine inhibition is caused by strychnine (Chap. 108 and Table 19–1).

Disorders of Movement and Tone

Most movement disorders (Table 19–2), including akathisia, bradykinesia, tics, dystonias, and chorea, are mediated by the complex dopaminergic pathways of

TABLE 19–1. Xenobiotic-Induced Seizures

Analgesics and nonprescription preparations
- Antihistamines
- Caffeine
- Mefenamic acid
- Phenylbutazone
- Salicylates

Prescription medications
- Antihistamines
- Bupropion
- Carbamazepine
- Chlorambucil
- Chloroquine
- Clonidine
- Digoxin
- Ergotamines
- Fenfluramine
- Isoniazid
- Lidocaine
- Methotrexate
- Phenytoin
- Procarbazine
- Quinine (cinchonism)
- Sulfonylureas
- Theophylline
- Tramadol

Psychopharmacologic medications
- Antiemetics
- Antipsychotics
- Cyclic antidepressants
- Lithium
- Methylphenidate
- Monoamine oxidase inhibitors (esp w/food or drug reaction)
- Opioids (propoxyphene, meperidine)
- Pemoline
- Sedative-hypnotic withdrawal

Alcohols and drugs of abuse
- Amphetamines
- Cocaine
- Disulfiram reaction
- Ethanol withdrawal
- Ethylene glycol

Botanicals
- Ackee fruit
- Cicutoxin
- *Coprinus* spp (disulfiram-like reaction w/alcohol)
- Daphne
- Herbal preparations (Lobelia, jimson weed, Galega, mandrake, passion flower, periwinkle, wormwood) (see Chaps. 43, 77, 114)
- Nicotine
- Rhododendron

Heavy metals
- Arsenic
- Copper
- Lead
- Manganese
- Nickel

Household toxins
- Boric acid (chronic)
- Camphor
- Fluoride
- Hexachlorophene
- Phenol

Pesticides
- Organochlorines (lindane)
- Organic phosphorous compounds
- Pyrethrins
- Rodenticides (thallium, sodium monofluoroacetate, strychnine, zinc phosphide, arsenic)
- Tetramethylenedisulfotetramine (TETS)

Occupational and environmental toxins
- Carbon disulfide
- Carbon monoxide
- Chlorphenoxy herbicides
- Cyanide
- Hydrocarbons
  - Simple asphyxiants (methane, ethane, propane, butane, natural gas)
  - High volatility (benzene, toluene, gasoline, naphtha, mineral spirits, light gas oil)
  - Halogenated (carbon tetrachloride, trichloroethane)
- Hydrogen sulfide
  - Toxic inhalants (simple asphyxiants producing hypoxia–helium, nitrogen, nitrous oxide)
- Triazine

(continued)

TABLE 19–1. Xenobiotic-Induced Seizures *(continued)*

Alcohols and drugs of abuse *(cont)*	**Toxic envenomation and marine animal ingestion**
MDMA (methylenedioxy-methamphetamine)	Marine animals (Gymnothorax, saxitoxin [shellfish])
Methanol	Pit viper
Phencyclidine	Scorpion
	Tick bite (*Rickettsia rickettsii*)

the basal ganglia. Different dopamine receptor subtypes, modulated by GABA-ergic, glutamatergic, and cholinergic neurons, are involved (Chap. 14).

Dopamine receptor antagonists can precipitate acute dystonic reactions. The D_2-receptor antagonists, in conjunction with alterations in muscarinic cholinergic tone, are usually implicated. Chorea occurs in some cases of carbamazepine overdose, therapeutic oral contraceptive use, and after cocaine use, when the stimulant effects have subsided. Other centrally mediated disorders of tone include serotonin syndrome and neuroleptic malignant syndrome (NMS) (Chap. 67).

Xenobiotic-Induced Parkinson Syndrome

Similar to idiopathic Parkinson syndrome, xenobiotic-induced Parkinson syndrome is defined by the clinical syndrome of unstable posture, rigidity, gait disturbance, loss of facial expression, and hypokinesis. The common neuroanatomic target involves the dopaminergic neurons of the basal ganglia, specifically the substantia nigra (Table 19–3).

TABLE 19–2. Xenobiotic-Induced Movement Disorders

Chorea	Dystonia	Dyskinesia	Akathisia
Anticholinergics	Anticonvulsants	Antipsychotics	Antidepressants
Anticonvulsants	Antiemetics	Calcium channel blockers	Selective serotonin reuptake inhibitors
Carbamazepine	Metoclopramide	Flunarizine	Cyclic antidepressants
Phenobarbital	Prochlorperazine	Cinnarizine	Phenelzine
Phenytoin	Antipsychotics	Fluvoxamine	Antiemetics
Antiparkinsonians	Fluvoxamine	Orthopramides and substituted benzamides	Metoclopramide
Amantadine	Levodopa	Clebopride	Prochlorperazine
Bromocriptine		Metoclopramide	Antipsychotics
Levodopa		Sulpride	Calcium channel blockers
Pergolide		Veralipride	Flunarizine
Antipsychotics			Cinnarizine
Carbon monoxide			Dopamine storage and transport inhibitors
Corticosteroids			α-Methyltyrosine
Ethanol			Reserpine
Lithium			Tetrabenazine
Manganese			
Metoclopramide			
Oral contraceptives			
Sympathomimetics			
Thallium			
Toluene			

TABLE 19–3. Xenobiotic-Induced Parkinsonism

Reversible[a]	Irreversible
Amlodipine	Carbon disulfide
Cyclosporine	Carbon monoxide
Calcium channel blockers	Copper
Dopaminergic withdrawal	Cyanide
Chemotherapeutics (numerous)	Heroin
Progesterone	Manganese
Sertraline	MPTP
Valproate	
Trazodone	

[a]Improved with removal of xenobiotic, sometimes requiring persistent administration of dopaminergic therapy.

TABLE 19–4. Classification of Selected Xenobiotic-Induced Peripheral Neuropathies

Neuronopathy	Axonopathy	Myelinopathy	Transmission Neuropathy
Acute toxic neuropathies			
Pyridoxine (S)	Hexacarbons (SMA) Thallium (SM) Triorthocresyl phosphate (SM) Vacor (MA)	Arsenic (SM) Diphtheria (SM)	Black widow spider Botulism Ciguatoxin Elapid and crotaline venoms Gymnothoratoxin Nicotine Saxitoxin Scorpion venom Tetrodotoxin Tick paralysis
Subacute/chronic toxic neuropathies			
None convincingly demonstrated	Acrylamide (SM) Allyl chloride (SM) Arsenic (SM) Buckthorn (M) Carbon disulfide (SM) Colchicine (S) Disulfiram (SM) Dapsone (M) 2'-3'-Dideoxycytidine (ddC), ddI Ethanol (M) Ethambutol (S) Ethionamide (S) Ethylene oxide (SM) Gold (SM)	5-Fluorouracil Amiodarone (SM) Amphotericin B methyl ester Amygdalin Buckthorn Cyclosporine Diethylene glycol Diphtheria (SM) Fludarabine Gold (SM) Hexachlorophene Interferon Levamisole Methotrexate Nitrous oxide	

(continued)

TABLE 19–4. Classification of Selected Xenobiotic-Induced Peripheral Neuropathies *(continued)*

Neuronopathy	Axonopathy	Myelinopathy	Transmission Neuropathy
Subacute/chronic toxic neuropathies *(cont)*			
	Hexacarbons (SM) Hydralazine (SM) Hydroxychloroquine Interferon-α Isoniazid (SM) Linezolid Methyl bromide (SM) Mercury (M) Methanol Nucleoside analogs Nitrofurantoin (SM) Nitrous oxide (S) Organic phosphorus compounds (SM) Polychlorinated biphenyls (SM) Phenytoin (SM) Platinum (S) Podophylin (SM) Taxol (S) Thallium (SM) Vincristine (SM)	Podophyllin Procainamide Tacrolimus Trichlorethylene (SM) Trovafloxacin L-Tryptophan Tumor necrosis factor-α Vacor (PNU) Vincristine Zinc	

A = autonomic; M = motor; S = sensory.

Peripheral Neuropathies

Patients with peripheral neuropathies may complain of pain, paresthesia, numbness, or weakness of their extremities. Common to most xenobiotic-induced neuropathies is early and symmetrical involvement of the lower extremities. This may be partly a result of the patient's rapid recognition of impairment during an attempt to ambulate. Additionally, the axons serving the lower extremities are longer. Maintenance and transportation of substrates are more energy dependent and sensitive to xenobiotic-induced disruptions. Neuronopathy, in which the cell body is damaged or destroyed, is typically irreversible. Axonopathy, the most common mechanism of xenobiotic-induced peripheral neuropathy, involves axonal dysfunction and is potentially reversible. Myelinopathy, or demyelination, may also occur. Transmission neuropathy is caused by xenobiotics that alter the synthesis, release, metabolism, or postsynaptic effects of neurotransmitters in the peripheral nerves (Table 19–4).

20 Ophthalmic Principles

The eye is a roughly spherical structure referred to as a globe. Xenobiotics can affect the eyes in diverse manners. The eyes may be injured by direct contact, may provide a portal of entry for xenobiotics with systemic toxicity, and may themselves be adversely affected by systemic exposures. Toxin-mediated injury to any of its structures can lead to symptoms as mild as chemical conjunctivitis or as severe as permanent blindness. Examination of the eye not only provides clues to the diagnosis of certain toxic exposures, but may also lead to timely detection of life-threatening indirect effects, such as intracranial hemorrhage.

OPHTHALMIC EXAMINATION

The routine eye examination is performed in the following sequence: visual acuity, pupillary light response, extraocular muscle function, funduscopy, and when indicated, a slit-lamp examination. Pupillary size and response to light can help determine a toxic syndrome. Opioids and cholinergics may produce miosis, whereas anticholinergics may produce mydriasis. Assessment of the extraocular muscles can reveal drug-induced nystagmus. Funduscopy can reveal pink discs characteristic of poisoning by methanol or systemic toxins such as carbon monoxide. The slit-lamp examination allows for evaluation of toxic exposure to the lids, lacrimal systems, conjunctiva, sclera, cornea, and anterior chamber.

Visual Acuity and Color Perception

Normal vision is dependent on light transmission to intact neural elements. Appropriate light transmission requires a clear cornea and aqueous humor, proper pupil size, an unclouded lens, and clear vitreous. The neural elements include the retina, optic nerve, and the optic cortex, and all of these structures require intact circulation for proper function. Decreased acuity can result from abnormalities anywhere in the visual system that affect either light transmission or neural elements. Corneal injury or edema may result in blurring of vision, characteristically described as "halos" around lights. Mydriasis secondary to various xenobiotics (Table 20–1) may interfere with the pupillary constriction necessary for accommodation, thereby resulting in decreased acuity for near objects. Lens clouding or cataract formation causes blurred vision and decreased light perception, as does blood (hyphema or hypopion) and other deposits in the aqueous or vitreous humors. Drug-induced lens abnormalities caused by chronic exposures are well described (Table 20–2) but are not important in acute toxicologic emergencies. Even if light reaches the retina without distortion, abnormal reception or transmission can result from ischemia or injury to any neural element from the retina to the optic cortex. Direct, acute visual neurotoxic injury is rare and is caused almost exclusively by methanol or quinine. Indirect injury following drug-induced CNS ischemia or hypoxia is far more common. Alterations in color perception generally result from abnormalities in retinal or optic nerve function. Color vision abnormalities are attributed to hundreds of xenobiotics, but unlike those

TABLE 20–1. Ophthalmic Findings Caused by Acute Xenobiotic Exposures

Miosis
- Increased cholinergic tone
  - Carbachol
  - Cholinesterase inhibitors (carbamates, organic phosphorus compounds)
  - Muscarine
  - Nicotine
  - Pilocarpine
- Decreased sympathetic tone (clonidine, guanabenz, methyldopa, opioids)
- Coma from sedative-hypnotics (barbiturates, benzodiazepines, ethanol)

Mydriasis
- Decreased cholinergic tone
  - Antihistamines
  - Belladonna alkaloids
  - Cyclic antidepressants (inconsistent finding)
  - Postanoxic encephalopathy
- Increased sympathetic tone (amphetamines, cocaine, phenylephrine and other sympathomimetics, ethanol and sedative-hypnotic withdrawal)

Nystagmus
- Carbamazepine
- Dextromethorphan
- Ethanol
- Ketamine
- Lithium
- Monoamine oxidase inhibitors
- Phencyclidine
- Phenytoin
- Sedative-hypnotics
- Thiamine deficiency

Dysconjugate gaze
- Botulism
- Elapid envenomation
- Neuromuscular blockers
- Paralytic shellfish poisoning
- Tetrodotoxin
- Thiamine deficiency
- Secondary to decreased level of consciousness (many causes)

Funduscopic abnormalities
- Carbon monoxide (red)
- Cocaine (vasoconstriction)
- Cyanide (retinal vein arteriolization)
- Ergot alkaloids (vasoconstriction)
- IV drug use (embolic)
- Methanol (disc and retinal pallor or hyperemia)
- Methemoglobin (cyanotic)

Papilledema
- See causes of pseudotumor cerebri (idiopathic intracranial hypertension)

TABLE 20–2. Examples of Ocular Abnormalities Caused by Chronic Systemic Xenobiotic Exposures[a]

Corneal/conjunctival inflammation
- Cytosine arabinoside (Ara-C)
- Isotretinoin[b]
- Mercury (acrodynia)
- Practolol[c]

Retinal injury
- Carmustine[c]
- Carbon disulfide[d]
- Chloramphenicol[c]
- Chloroquine
- Cinchona alkaloids (quinine)
- Deferoxamine[c]
- Digitalis[c]
- Ethambutol
- Thallium
- Vigabatrin
- Vincristine[c]

Uveitis
- Bisphosphonates
- Pamidronate
- Rifabutin
- Sulfonamides

Corneal deposits
- Amiodarone[b]
- Chloroquine
- Chlorpromazine
- Copper[d]
- Gold
- Mercury[d]
- Retinoids
- Silver (argyria)[d]
- Vitamin D

Retrobulbar and optic neuropathy
- Carbon disulfide[d]
- Chloramphenicol[d]
- Dinitrobenzene[d]
- Dinitrochlorobenzene[d]
- Dinitrotoluene[d]
- Disulfiram
- Ethambutol[b]
- Isoniazid[c]
- Lead[c]
- Thallium
- Vincristine[c]

Cataracts
- Busulfan[c]
- Corticosteroids[b]
- Deferoxamine
- Dinitrophenol (internal use)[d]
- Trinitrotoluene[d]

Cortical blindness
- Cisplatin
- Cyclosporine
- Interleukin[c]
- Tacrolimus
- Methylmercury compounds[d]

Lens deposits
- Amiodarone[b]
- Chlorpromazine
- Copper[d]
- Iron
- Mercury[d]
- Silver[d]

Myopia[c]
- Acetazolamide
- Diuretics (chlorthalidone, thiazides, spironolactone)
- Retinoids
- Sulfonamides

[a]This list includes only selected examples and is not intended to be comprehensive.
[b]Particularly important example.
[c]Reported, but extremely rare from this exposure.
[d]Mostly of historical interest; associated with patterns of use that are no longer common.

caused by chronic drug exposure, such abnormalities are rare and inconsistent features of acute toxicity.

Pupil Size and Reactivity

Generally, pupils are round and symmetric with an average diameter of 3–4 mm under typical light conditions. Pupils react directly and consensually to light intensity by either constricting or dilating. The iris controls pupil size through a balance of cholinergic innervation of the sphincter (constrictor) muscle by cranial nerve III and sympathetic innervation of the radial (dilator) muscle.

Pupillary dilation (mydriasis) can result from increased sympathetic stimulation by endogenous catecholamines or from xenobiotics such as cocaine, amphetamines, and other sympathomimetics. Mydriasis can also result from inhibition of muscarinic cholinergic-mediated pupillary constriction secondary to systemic or ophthalmic exposure to anticholinergics. Because pupillary constriction in response to light is a major determinant of normal pupil size, blindness from ocular, retinal, or optic nerve disorders also leads to mydriasis. Light reactivity is absent in cases of complete blindness caused by retinal or optic nerve damage but may be preserved if there is some remaining light perception.

Miosis can result from increased cholinergic stimulation such as opioids, pilocarpine, and anticholinesterases such as organic phosphorus agents, or from inhibition of sympathetic dilation caused by clonidine. For some substances, the pupillary examination provides consistent information (Table 20–1), but many factors are involved and the significance of the pupil size and reactivity must always be considered in the context of the remainder of the patient evaluation.

Extraocular Movement, Diplopia, and Nystagmus

Maintenance of normal eye position and movement requires a coordinated function of a complex circuit involving bilateral frontal and occipital cortices, multiple brainstem nuclei, cranial nerves, extraocular muscles, and connecting fibers between each. Probably the most common abnormality of eye movement is reversible nystagmus (Table 20–1). Drug-induced nystagmus may take many forms but is most commonly jerk nystagmus, as opposed to pendular, or horizontal and symmetric. Drug-induced vertical nystagmus occurs with cocaine, phencyclidine, ketamine, dextromethorphan, or phenytoin toxicity; however, vertical nystagmus is usually associated with a structural lesion of the CNS. Loss of conjugate gaze commonly results from CNS depression of any cause, typically after a sedative-hypnotic or ethanol overdose. Except after extremely rare exposures to neurotoxins (Table 20–1), diplopia without a decreased level of consciousness should *not* be attributed to an acute toxicologic etiology.

SYSTEMIC ABSORPTION AND TOXICITY FROM OCULAR EXPOSURES

Systemic absorption from ocular exposures has caused serious toxicity, morbidity, and death. Although transcorneal diffusion of drug is limited, there is substantial nasal mucosal absorption after nasolacrimal drainage, and absorption via conjunctival capillaries and lymphatics, which is markedly increased

during conjunctival inflammation. Unlike the gastrointestinal route of absorption, there is no significant first-pass hepatic removal after ocular absorption and, therefore, bioavailability is much greater. If nasolacrimal outflow is normal, up to 80% of instilled drug may be absorbed systemically. Children appear to be at greatest risk, possibly because of the higher relative drug dose they experience when systemic absorption occurs.

Mydriatics, Miotics, and Antiglaucoma Drugs

Mydriatics are used to dilate the pupils prior to diagnostic evaluation of the eyes. Anticholinergic poisoning is well described after ocular use, especially in infants. The use of the α-adrenergic agonist eyedrops phenylephrine in a 10% solution can cause severe hypertension, subarachnoid hemorrhage, ventricular dysrhythmias, and myocardial infarction. These effects are rare if the 2.5% ocular phenylephrine is used. Mydriatics can also precipitate acute angle closure glaucoma in susceptible individuals.

Maintaining miosis to prevent angle closure is an important part of glaucoma therapy. Cholinesterase inhibitors, such as echothiophate, can exacerbate asthma, parkinsonism, peptic ulcer disease, and cardiac disease. If succinylcholine and mivacurium are used to produce neuromuscular blockade in patients using ocular cholinesterase inhibitors, prolonged paralysis can occur. Miosis can also be produced by use of direct cholinergic agonists, such as pilocarpine, which have a much shorter duration of action. Although absorption is limited, nausea and abdominal cramps can occur at recommended doses. After excessive dosing, salivation, diaphoresis, bradycardia, and hypotension may occur.

β-Adrenergic antagonists, such as timolol, levobunolol, metipranolol, carteolol, and betaxolol, are used to lower intraocular pressure but cause a variety of adverse effects, including bradycardia, hypotension, myocardial infarction, syncope, transient ischemic attacks, congestive heart failure, exacerbation of asthma, status asthmaticus, respiratory arrest, myasthenia gravis, and masking symptoms of hypoglycemia. Dipivefrin, an esterified epinephrine derivative sometimes used to treat glaucoma, can cause adrenergic systemic effects, although much less than those of epinephrine. Systemic absorption of brimonidine eye drops in a child has led to bradycardia, hypotension, and decreased level of consciousness, similar to the central effects of other α_2-adrenoceptor agonists, apparently mediated through both α_2-adrenoceptors and imidazoline receptors.

Antimicrobials

Life-threatening reactions to ophthalmic antimicrobials are unusual but do occur. Episodes of aplastic anemia have occurred after prolonged use of chloramphenicol eye preparations, and Stevens-Johnson syndrome was reported after short-term use of ophthalmic sulfacetamide in a patient with a history of allergy to sulfa drugs.

OCULAR CAUSTIC EXPOSURES: FIRST AID AND INITIAL APPROACH

The initial approach to all patients with ocular caustic exposures should be immediate decontamination by irrigating with copious amounts of fluids, water being the most often used. Water, 0.9% sodium chloride solution, lactated

Ringer solution, and balanced salt solution (BSS) are all appropriate choices. The use of an ocular anesthetic is usually required to perform irrigation properly. Irrigation is intended to accomplish at least four objectives: immediate dilution of the offending xenobiotic, removal of the xenobiotic, removal of any foreign body, and, in some cases, normalization of anterior chamber pH. As delays of even seconds can dramatically affect outcome, there is no justification for waiting for any specific solution if water is available. Effective irrigation includes lid retraction and eversion or use of a scleral shell or other irrigating device. After irrigation, visual acuity testing, inspection of the eye, and slit-lamp examination should be performed.

Duration of Irrigation

To accomplish the desired goals of irrigation, the appropriate duration varies with the exposure. Most solvents, for example, do not penetrate deeper than the superficial cornea, and brief (10–20 minutes) irrigation is generally sufficient. After exposure to acids or alkalis, normalization of the conjunctival pH is often suggested as a useful end point. Testing of pH should be done in every case of acid or alkali exposure, but the limitations of testing must be understood. When measured by sensitive experimental methods, normal pH of the conjunctival surface is 6.5–7.6; however, normal values in the literature range from 5.2–8.6. When measured by touching pH-sensitive paper to the moist surface of the conjunctival cul-de-sac, normal pH is most often near 8. Therefore, after irrigation following alkali burns, pH should not be expected to reach 7 and is more likely to stabilize near 8.

Despite these limitations, a logical role for pH assessment can be described: probably a minimum of 500–1000 mL of irrigant should be used for each affected eye before any assessment of pH; and then, after 7–10 minutes, the pH of the lower fornix conjunctiva should be checked. Thereafter, cycles of 10–15 minutes of irrigation followed by rechecks should be continued until the pH is 7.5–8. For strong alkaline or acid, irrigation should be continued for at least 2–3 hours, regardless of surface pH, in an attempt to correct anterior chamber pH, and immediate ophthalmologic consultation is mandatory. Following this lengthy irrigation, it is important to verify that conjunctival pH has normalized. If not, irrigation must be continued, sometimes for 24–48 hours.

OCULAR CAUSTIC EXPOSURES: SPECIFIC XENOBIOTICS

The effect of any chemical on the eye depends on the inherent properties of the xenobiotic, be it a solvent or detergent; the amount, concentration, and pH of the xenobiotic; and the duration of exposure. The end result of ocular exposure to these xenobiotics depends on the extent of damage to the cornea, particularly the integrity and function of the stroma; chemical penetration into the anterior chamber and the resulting injury to its structures; and resultant inflammatory reaction.

Acids and Alkalis

Fortunately, weak acids do not penetrate the cornea well. The hydrogen ion causes damage by lowering ocular pH, whereas the anion denatures ocular proteins on contact, causing precipitation and coagulation that actually limits the extent of penetration. Hydrofluoric acid may cause unexpectedly severe injury because of its ability to penetrate deep into the eye.

Alkali burns of the eye represent an ophthalmic emergency. The hydroxyl ion saponifies lipid membranes, directly disrupting cells, while the penetration of the alkali is determined by the cation. Cations react with and hydrate stromal collagen and glycosaminoglycans, causing loss of clarity. For this reason, once the damaged epithelium is swept away, any haziness of the underlying stroma is evidence of alkali penetration and potential serious sequelae.

The full extent of injury may not be evident for 48–72 hours. In the ensuing days to weeks, outcome is determined by the balance between degradation and repair of the stromal matrix, the quantity and quality of corneal reepithelialization, and the extent of inflammatory cell infiltration. After severe burns, normal repair is distinctly rare and extensive scarring is the rule. The goal of therapy is to prevent corneal ulceration, ocular perforation, and glaucoma while preserving the eye for possible secondary surgical revision or repair.

Other Chemical Exposures

Most solvents cause immediate pain and superficial injury because of dissolution of corneal epithelial lipid membranes, but do not penetrate or react significantly with deeper tissue. The epithelial defect may be large or complete, but the limited depth of injury usually allows rapid regeneration of normal epithelium. Pepper spray, often used for self-protection by civilians or law-enforcement agents, contains the active ingredient oleoresin capsicum (OC). OC results in rapid depolarization of nociceptors containing substance P, resulting in immediate pain, blepharospasm, tearing, and blurred vision. In general, ocular injury is uncommon, although corneal erosions can occur. Management of pepper spray exposure consists of rapid irrigation and pain control.

TABLE 20–3. Xenobiotics Reported to Cause Visual Loss after Acute Exposures

Direct causes
Caustics
Methanol
Quinine
Lead[a]
Mercuric chloride[a]
Indirect causes[b]
Amphetamines
Cocaine
Embolization of foreign material (parenteral injection)
Cisplatinum
Combined endocrine agents (thyrotropin-releasing hormone with gonadotropin-releasing hormone and glucagon)
Ergot alkaloids
Hypotension (eg, calcium channel blockers)

[a]Distinctly rare with these poisonings.
[b]Distinctly rare with use of these agents; visual loss often instantaneous, secondary to sudden hypotension, vascular spasm, or embolization.
Adapted, with permission, from Smilkstein MJ, Kulig KW, Rumack BH: Acute toxic blindness: Unrecognized quinine poisoning. Ann Emerg Med 1987;16:98–101.

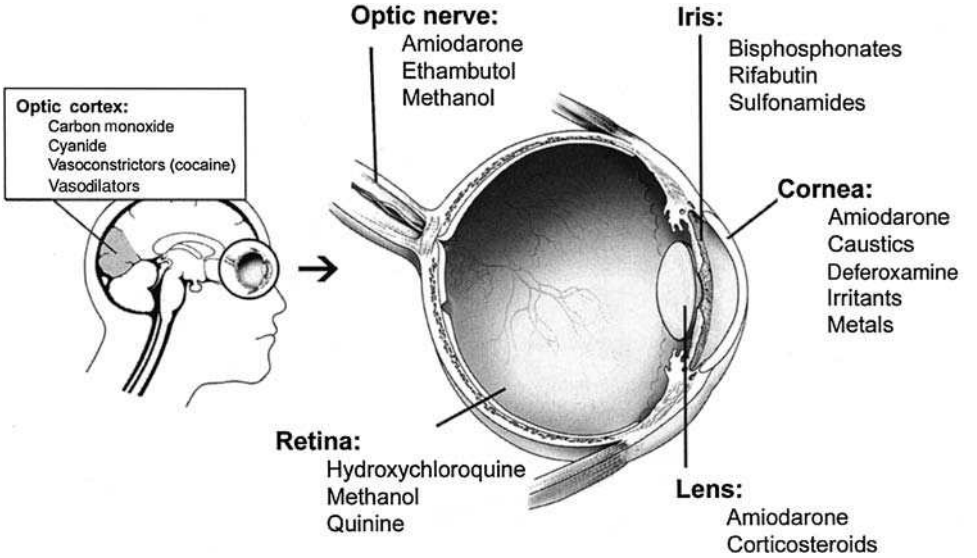

FIG. 20–1. Summary of ocular effects of systemic exposures. (Courtesy of the National Eye Institute, National Institutes of Health, adapted by Joseph Lewey.)

DISPOSITION

Patients with extensive burns to other parts of the body should be evaluated for transfer to a burn center. Grading the degree of injury in patients with isolated ocular injury can guide disposition. The most commonly used grading system is the Roper-Hall modification of the Ballen classification system. Injury is graded on a 4-tier scale; patients with mild conjunctival injection with corneal epithelial loss and minimal corneal haziness are classified as grades 1 and 2 (mild to moderate). These patients can be safely discharged from the emergency department with ophthalmology followup within 24–48 hours. Patients with severe corneal haziness or opacification with significant limbal ischemia are classified as grades 3 or 4 (moderate to severe) and should receive immediate consultation with an ophthalmologist and transfer to a burn unit should be considered.

TOXICITY TO OCULAR STRUCTURES FROM NONOCULAR EXPOSURES

Ocular toxicity from systemic agents is almost always the result of chronic exposure, and the manifestations develop over a prolonged period of time. Thousands of substances are implicated, affecting every element of the visual system from the cornea to the optic cortex. Thorough discussion of this topic is beyond the scope of this text, but Table 20–2 lists examples of causative xenobiotics.

In the setting of emergency care, xenobiotic-induced disturbances of normal vision from systemic exposures take many forms. Impaired near-vision from mydriasis, and diplopia or nystagmus from interference with normal control of extraocular movements, are examples of common, usually harmless, visual effects. Serious effects generally result from injury or dysfunction of the neural elements from the retina to the cortex. Such toxicity can be direct (neurotoxic) or indirect (hypoxia, ischemia). Many xenobiotics historically reported to cause acute visual loss directly are no longer available (Table 20–3). Figure 20–1 summarizes the ocular effects of systemic exposures.

21 Otolaryngologic Principles

Many xenobiotics adversely affect the special senses of olfaction, gustation, and cochlear-vestibular functions. These toxic effects are not life-threatening and frequently not considered of substantial importance.

OLFACTION

A number of problems result from the impact of smell as a toxicologic warning system. Human olfaction is a variable trait. For example, 40–45% of people have specific anosmia (inability or loss of smell) for the bitter almond odor of cyanide. Olfactory fatigue is the process of olfactory adaptation following exposure to a stimulus for a variable period of time. Unfortunately, this adaptation may lead to a false sense of security with continued exposure to a toxin, such as hydrogen sulfide. The combination of the rapid onset of olfactory fatigue and toxicity at high concentrations of hydrogen sulfide exposure has contributed to numerous fatalities (Chap. 121).

Etiology of Olfactory Impairment

Chronic exposures to numerous xenobiotics are associated with olfactory dysfunction (Table 21–1).

GUSTATION

Etiology of Gustatory Impairment

Types of gustatory dysfunction include ageusia, the inability to perceive taste, hypogeusia, the diminished sensitivity of taste; and dysgeusia, the distortion of normal taste. There are several variations of dysgeusia, such as cacogeusia, which is a perceived foul, perverted, or metallic taste. Taste impairment is commonly related to direct damage to the taste receptors, adverse effects on their regeneration, or effects on receptor mechanisms. These effects can result from various xenobiotics, diseases, aging, and nutritional disorders (Table 21–2).

HEARING

Xenobiotic-Induced Ototoxicity

Ototoxicity includes effects on the cochlear and vestibular system. Many xenobiotics have been implicated as ototoxins, some of which cause reversible ototoxicity, whereas others cause irreversible toxicity (Table 21–3). Ototoxic xenobiotics primarily affect two different sites in the cochlea: the organ of Corti, specifically the outer hair cells, and the stria vascularis. Because of the limited regenerative capacity of the sensory hair cells and other supporting cells, when significant cellular damage occurs, the loss is often permanent. Whereas cell death of the outer hair cells from inflammation and necrosis are expected when sufficient insults occurrs, apoptotic cell death is now postulated to be a major mechanism of ototoxicity from certain xenobiotics such as cisplatin and aminoglycosides. Inhibition of caspases and calpain associated with apoptosis of the hair cells decreases ototoxicity from cisplatin and aminoglycosides in animals. Loop diuretics, such as furosemide, bumetanide, and ethacrynic acid, cause physiologic dysfunction and edema at the stria vascularis, resulting in reversible hearing loss. The underlying

TABLE 21–1. Differential Diagnosis of Xenobiotics Responsible for Disorders of Smell

Hyposmia/Anosmia	Dysosmia/Cacosmia/Phantosmia
Acrylic acid	Amebicides/antihelminthics: metronidazole
Antihyperlipidemics	Anesthetics, local: varied
Cholestyramine	Anticonvulsants
Clofibrate	Carbamazepine
Gemfibrozil	Phenytoin
HMG-CoA reductase inhibitors	Antihistamines
Cadmium	Antihypertensives
Chlorhexidine	ACE inhibitors
Cocaine	Diazoxide
Formaldehyde	Antimicrobials
Gentamicin nose drops	Antiinflammatory/antirheumatics: allopurinol, colchicine, gold, D-penicillamine
Hydrocarbons (volatile)	
Hydrogen sulfide	Antiparkinson agents
Methylbromide	Levodopa
Nutritional	Bromocriptine
Vitamin B_{12} deficiency	Antithyroid agents
Zinc deficiency	Methimazole
Pentamidine	Methylthiouracil
Sulfur dioxide	Propylthiouracil
	β-Adrenergic antagonists
	Calcium channel blockers
	Dental: tooth pastes
	Diuretics: ethacrynic acid
	DMSO (dimethylsulfoxide)
	Insecticides
	Lithium
	Nicotine
	Opioids: varied
	Sympathomimetics: varied
	Vitamin D

Definitions: Anosmia = the loss of smell; cacosmia = sensation of a foul smell; dysosmia = a distorted perception of smell; hyposmia = a decreased perception of smell; phantosmia = sensation of smell without stimulus.

mechanisms appear to be the inhibition of potassium pumps and G proteins associated with adenyl cyclase.

Salicylate-induced hearing loss is generally mild to moderate (20–40 dB loss) and reversible. The mechanism of salicylate-induced ototoxicity is unclear, although multiple factors are postulated. Salicylates and other NSAIDs inhibit cyclooxygenase, which convert arachidonic acid to prostaglandin G_2 and prostaglandin H_2. These effects may interfere with Na^+-K^+-adenosine triphosphatase (ATPase) pump function at the stria vascularis and also decrease cochlear blood flow. Reversible decrease in outer hair cell turgor secondary to membrane permeability changes may impair otoacoustic emissions. NSAIDs and the cinchona alkaloid quinine also cause reversible hearing loss, particularly at the higher frequencies. The primary mechanism is related to prostaglandin inhibition.

The aminoglycosides are the best known group of drugs associated with irreversible ototoxicity. The reported rates of ototoxicity for the more commonly used aminoglycosides gentamicin and tobramycin are between 5% and 8%. The risks of ototoxicity are increased with a duration of therapy of

TABLE 21–2. Xenobiotics Responsible for Alterations of Taste

Hypogeusia/ageusia		
Local		
Chemical burn		
Radiation therapy		
Systemic		
ACE inhibitors	DMSO (dimethyl-sulfoxide)	Propranolol
Amiloride	Gasoline	Pyrethrins
Amrinone	Hydrochlorothiazide	Smoking
Carbon monoxide	Methylthiouracil	Spironolactone
Cocaine	Nitroglycerin	Triazolam
	NSAIDs	
	Penicillamine	
Dysgeusia		
Local		
Chemical burn		
Radiation therapy		
Systemic		
ACE inhibitors	DMSO (dimethyl-sulfoxide)	NSAIDs
Adriamycin	5-Fluorouracil	Nicotine
Amphotericin B	Griseofulvin	Nifedipine
Botulism (in recovery)	Isotretinoin	Quinine
Bretylium	Levodopa	Zinc deficiency
Carbamazepine		
Metallic taste		
ACE inhibitors	Ethambutol	Metronidazole
Acetaldehyde	Ferrous salts	Pentamidine
Allopurinol	Flurazepam	Procaine penicillin
Arsenicals	Iodine	Propafenone
Cadmium	Lead	Snake envenomation
Ciguatoxin	Levamisole	Tetracycline
Copper	Lithium	
Coprinus spp	Mercury	
Dipyridamole	Methotrexate	
Disulfiram	Metoclopramide	

longer than 10 days, concomitant use of other ototoxic xenobiotics, and the development of elevated serum concentrations. There is no evidence that single daily dosing of aminoglycosides alters the risk of ototoxicity. Loop diuretics increase aminoglycoside toxicity by increasing aminoglycoside penetration into the endolymph.

Bromates are among the most extensively studied ototoxic xenobiotics. Bromates are used in hair neutralizers, bread preservatives, and as fuses in explosive devices. The stria vascularis and hair cells of the organ of Corti can be irreversibly damaged with significant exposure. Bromates may also cause renal failure with substantial exposure, perhaps increasing the ototoxic potential.

It is intriguing that xenobiotics such as the bromates and aminoglycosides primarily affect both the cochlea and the kidneys. One possible explanation is that the stria vascularis and the renal tubules have similar functions in main-

TABLE 21–3. Etiologies of Xenobiotic-Induced Hearing Loss

Reversible
Antimicrobials: chloroquine, erythromycin, quinine
Carbon monoxide
Diuretics: acetazolamide, bumetanide, ethacrynic acid, furosemide, mannitol
NSAIDs
Salicylates
Irreversible
Aminoglycosides
Antineoplastics: bleomycin, cisplatin, nitrogen mustard, vincristine, vinblastine
Bromates
Hydrocarbons: styrene, toluene, xylene
Metals: arsenic, lead, mercury

taining electrochemical gradients. However, renal tubules may regenerate, whereas damage to the hair cells and the stria vascularis of the cochlea is more likely to be permanent.

Etiology of Tinnitus

Tinnitus is the sensation of sound not resulting from mechanoacoustic or electric signals. Virtually all humans experience tinnitus at some point in their life. Tinnitus may or may not be associated with hearing loss. Tinnitus may result from spontaneous neurologic discharges when the hair cells or cochlear nerve are injured. Altered sound perception may result from local or central effects when feedback mechanisms are interrupted. Severing the cochlear nerve terminates tinnitus in less than half of affected patients, suggesting important central mechanisms. Xenobiotics, including salicylates, may cause hair cell dysfunction and may modify neurotransmission centrally in

TABLE 21–4. Xenobiotics That Cause Tinnitus

Antifungals: amphotericin B
Anticonvulsants: carbamazepine
Antidepressants: cyclic antidepressants, amoxapine, lithium, trancylcypromine
Antihistamines
Antimicrobials: Aminoglycosides, vancomycin, dapsone, tetracyclines, sulfa drugs, metronidazole, thiabendazole, clindamycin
Antineoplastics: cisplatin, nitrogen mustard, 6-aminonicotinamide, methotrexate, vinblastine
Antiparasitics: chloroquine, hydroxychloroquine
Antipsychotics: haloperidol, molindone
β-Adrenergic antagonists
Bromates
Cinchona alkaloids: quinine, quinidine, salicylates
Diuretics: furosemide, ethacrynic acid, bumetanide
Hydrocarbons: benzene
Local anesthetics: mepivacaine, bupivacaine, lidocaine
NSAIDs
Oral contraceptives
Sympathomimetics: caffeine, theophylline, metaproterenol, albuterol, methylphenidate

both the cochlear nucleus and the inferior colliculis. For salicylate and NSAIDs, cyclooxygenase inhibition and resulting *N*-methyl-D-aspartate (NMDA) receptor activation is the likely mechanism for tinnitus.

Numerous xenobiotics are associated with tinnitus (Table 21–4), but the incidence is probably low and the implied relationships have usually been supported only by case reports. Tinnitus may or may not be associated with transient or permanent hearing loss. It is probable that these xenobiotics, also associated with hearing loss, affect cochlear function, while those that produce tinnitus without hearing loss probably act on signal transmission at the cochlear and the central nervous system. Xenobiotics that frequently produce tinnitus are streptomycin, neomycin, indomethacin, doxycycline, ethacrynic acid, furosemide, heavy metals, and high doses of caffeine. Only a few drugs, such as quinine and salicylates, consistently cause tinnitus at toxic doses.

Tinnitus associated with salicylates usually begins when serum concentrations are in the high therapeutic or low toxic range of approximately 20–40 mg/dL. Before the wide availability of salicylate serum measurements, physicians treating gout or rheumatoid arthritis often titrated the salicylate dosage until tinnitus developed. The classic constellation of symptoms of quinine and salicylate toxicity, called cinchonism, includes nausea, vomiting, tinnitus, and visual disturbances.

22 Respiratory Principles

The primary function of the lungs is to exchange gases. Specifically, this role can be divided into the transport of oxygen (O_2) into the blood and the elimination of carbon dioxide (CO_2) from the blood. In addition, the lungs serve as minor organs of metabolism and elimination for a number of compounds, a source of insensible water loss, and a means of temperature regulation.

Cellular oxygen use is dependent on many factors, including respiratory drive; percent oxygen in inspired air; airway patency; chest wall and pulmonary compliance; diffusing capacity; ventilation–perfusion mismatch; hemoglobin content; hemoglobin oxygen loading and unloading; cellular oxygen uptake; and cardiac output. Xenobiotics have the unique capability to inhibit or impair each of these factors necessary for oxygen use, which results in respiratory dysfunction.

PULMONARY MANIFESTATIONS OF XENOBIOTIC EXPOSURES

Respiratory Drive

Respiratory rate and depth are regulated by the need to maintain a normal PCO_2 and pH. Most of the control for ventilation occurs at the level of the medulla, although this is modulated both by involuntary input from the pons and voluntary input from the higher cortices. Xenobiotics can affect respiratory drive in one of several ways: direct suppression of the respiratory center; alteration in the response of chemoreceptors to changes in PCO_2; direct stimulation of the respiratory center; increase in metabolic demands as a result of agitation or fever, which, in turn, increases total body oxygen consumption; or indirectly, as a result of the creation of acid–base disorders. Any xenobiotic that causes a decreased respiratory drive or a decreased level of consciousness can produce bradypnea (a decreased respiratory rate), hypopnea (a decreased tidal volume), or both, which results in hypoventilation. Xenobiotics can cause an increase in respiratory drive, as well as an increase in oxygen consumption. The net consequence of increased respiratory drive, increased oxygen consumption, or metabolic acidosis is the generation of either tachypnea (an elevated respiratory rate), hyperpnea (an increased tidal volume), or both. Tables 22–1 and 22–2 list the xenobiotics that commonly produce hypo- or hyperventilation.

Decreased Inspired FiO_2

Barometric pressure at sea level ranges near 760 mm Hg. At this pressure, 21% of ambient air is comprised of oxygen (FiO_2 = 21%), and after subtracting for the water vapor normally present in the lungs, PAO_2 (the alveolar partial pressure of oxygen) is about 150 mm Hg. Any reduction in FiO_2 decreases the PAO_2, thereby producing signs and symptoms of hypoxemia (a low PaO_2 [the arterial partial pressure of oxygen]). At an FiO_2 of 12–16%, patients experience tachypnea, tachycardia, headache, mild confusion, and impaired coordination. A further decrease to an FiO_2 of 10–14% produces severe fatigue and cognitive impairment. Decreases to between 6% and 10% are associated with nausea, vomiting, and lethargy. An FiO_2 of less than 6% is incompatible with life.

TABLE 22–1. Xenobiotics That Produce Hypoventilation

Baclofen	Electrolyte abnormalities	Organic phosphorus compounds
Barbiturates	Ethanol	Poison hemlock (coniine)
Botulinum toxin	Ethylene glycol	Sedative-hypnotics
Carbamates	γ-Hydroxybutyrate	Strychnine
Clonidine	Isopropanol	Tetanus toxin
Colchicine	Methanol	Tetrodotoxin
Cyclic antidepressants	Neuromuscular blockers	
Elapid envenomation	Nicotine	
	Opioids	

This effect on FiO_2 is typically observed as elevation increases or in closed or low-lying spaces, when oxygen may be replaced or displaced by other gases that have no intrinsic toxicity. Table 22–3 lists some common examples of these gases, which are referred to as simple asphyxiants.

Chest Wall

Adequate ventilation is dependent on the coordination and function of the muscles of the diaphragm and chest wall. Changes in this function can result in hypoventilation by two separate mechanisms; both muscle weakness and muscle rigidity can impair the patient's ability to expand the chest wall.

Airway Patency

The airway itself may be compromised in several ways. As a patient's mental status becomes impaired, the airway is often obstructed by the tongue. Alternatively, vomitus, or either aspiration of activated charcoal or a foreign body, can directly obstruct the trachea or major bronchi with resultant hypoxia. Obstruction can also result from increased secretions produced during organic phosphorous compound poisoning. Laryngospasm may occur either as a manifestation of systemic reactions, such as anaphylaxis, as a result of edema from thermal or caustic injury, or as a direct response to an irritant gas. Regardless of the mechanism, upper airway obstruction results in hypoventilation, hypoxemia, and hypercapnia (hypercarbia) with the persistence of a normal A-a gradient.

Bronchospasm may be a manifestation of anaphylaxis, as well as exposure to numerous xenobiotics such as the irritant gases (Table 22–4). Airway collapse may result from pneumothorax caused by barotrauma, which more com-

TABLE 22–2. Xenobiotics That Produce Hyperventilation

Amphetamines	Gyromitra mushrooms	Paraldehyde
Anticholinergics	Hydrogen sulfide	Pentachlorophenol
Camphor	Iron	Phenformin
Carbon monoxide	Isoniazid	Progesterone
Cocaine	Isopropanol	Salicylates
Cyanide	Methanol	Sodium monofluoroacetate
Dinitrophenol	Metformin	
Ethanol (ketoacidosis)	Methemoglobin inducers	
Ethylene glycol	Methylxanthines	

TABLE 22–3. Simple Asphyxiants

Argon	Hydrogen
Carbon dioxide	Methane
Ethane	Nitrogen
Helium	Propane

monly results from the manner of administration of illicit drugs than from actual drug overdose. Barotrauma can also result from nasal insufflation or inhalation of drugs.

Ventilation–Perfusion Mismatch

Ventilation–perfusion (V/Q) mismatch is manifested at the extremes by aeration of the lung without arterial blood supply (as in pulmonary embolism from injected contaminants) and by a normal blood supply to the lung without any ventilation. In toxicology, V/Q mismatch most commonly results from perfusion of an abnormally ventilated lung, as may occur following aspiration of gastric contents, a frequent complication of many types of poisoning. Most commonly, aspiration occurs in the right mainstem bronchus, because the angle with the carina is not as acute as it is for entry into the left mainstem bronchus. When aspiration occurs in the supine position, the subsequent infiltrate is usually manifest in the posterior segments of the upper lobe and superior segments of the lower lobe.

Diffusing Capacity Abnormalities

Severe impairment in diffusing capacity commonly results from local injury to the lungs in disorders such as interstitial pneumonia, aspiration, toxic inhalations, and near drowning, and from systemic effects of sepsis, trauma, and various other medical disorders. When this process is acute and associated with clinical criteria, including rales, hypoxemia (unspecified degree), and bilateral involvement on a chest radiograph demonstrating a normal heart size, it has been traditionally referred to as noncardiogenic pulmonary edema; however, in this text, the term *acute lung injury* (ALI) is used instead, because it reflects current nomenclature. Acute lung injury may result from exposure to xenobiotics that produce hypoventilation by at least three different mechanisms: hypoxia may injure the vascular endothelial cells; autoregulatory vascular redistribution may cause localized capillary hypertension; or alveolar microtrauma may occur as alveolar units collapse, only to be reopened suddenly during reventilation. Acute lung injury is the presence of increased intraalveolar fluid in the lungs with a normal cardiac output. More rigid criteria, such as a PaO_2:FiO_2 ratio of <300 mm Hg (regardless of positive end-

TABLE 22–4. Irritant Gases

Ammonia	Isocyanates
Chloramine	Nitrogen dioxide
Chlorine	Ozone
Chloracetophenone (CN)	Phosgene
Chlorobenzylidene-malonitrile (CS)	Phosphine
Fluorine	Sulfur dioxide
Hydrogen chloride	

expiratory pressure [PEEP]), bilateral infiltrates on the chest radiograph, and either the pulmonary artery wedge pressure being ≤18 mm Hg or no clinical evidence of left atrial hypertension, are used to define the ALI. When these same criteria are met, but the patient's PaO_2:FiO_2 ratio is <200 mm Hg (regardless of PEEP), the term *acute respiratory distress syndrome* (ARDS) is used. Acute lung injury from opioids, salicylates, or phosgene, and delayed severe fibrosis from paraquat can all cause profound alterations in diffusion.

Cardiogenic pulmonary edema may also occur as the result of poisoning. Etiologies include the ingestion of large amounts of an agent with negative inotropy (eg, β-adrenergic antagonists, type IA antidysrhythmics) or myocardial infarction (from cocaine). Because many overdoses are mixed overdoses, the distinction between cardiogenic pulmonary edema and ALI is often difficult to establish by physical examination and may require invasive monitoring techniques.

The basic treatment for ALI and ARDS is supportive care while the xenobiotic is eliminated and healing occurs in the pulmonary capillaries. The most important specific therapeutic maneuver in patients with ALI/ARDS involves the use of low tidal-volume ventilation. This results in reduced airway pressures, which seem to "rest" the lung and allow healing to occur.

Hemoglobin and the Chemical Asphyxiants

Disorders of hemoglobin oxygen content, as well as of hemoglobin loading and unloading, result in cellular hypoxia, which, in turn, results in hyperventilation. Anemia is a common complication of the infectious diseases associated with parenteral drug use. In addition, many xenobiotics result in hemolysis or direct bone marrow suppression. Among the latter group are the heavy metals, lead, benzene, and ethanol. Hemolysis may occur in individuals exposed to lead, copper, or arsine gas, and in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency exposed to oxidants.

The oxygen-carrying capacity of blood declines in almost direct proportion to hemoglobin content. Under most normal conditions the dissolved oxygen content of the blood contributes little. In contrast, as the PO_2 reaches higher values (as in hyperbaric oxygen [HBO] chambers), the dissolved oxygen content becomes significant and may be of therapeutic value, particularly when the oxygen-carrying content of hemoglobin is compromised.

The chemical asphyxiants that produce methemoglobin, carboxyhemoglobin, and sulfhemoglobin all interfere with oxygen loading and/or unloading to various degrees. Methemoglobin inhibits oxygen loading, producing cyanosis that is unresponsive to supplemental oxygen. In addition, the oxyhemoglobin saturation curve is shifted to the left, interfering with unloading (Fig. 22–1). Carboxyhemoglobin has similar effects on oxygen loading and unloading, but carboxyhemoglobin is not associated with cyanosis.

Cardiac Output

Any xenobiotic that causes a decreased cardiac output or hypotension may result in tissue hypoxia and tachypnea. This occurs most frequently with overdoses of β-adrenergic antagonists and calcium channel blockers, antidysrhythmics, cyclic antidepressants, and phenothiazines.

APPROACH TO THE POISONED PATIENT

The initial assessment of every patient must involve the evaluation of upper airway patency. Then adequacy of ventilation should be determined. When

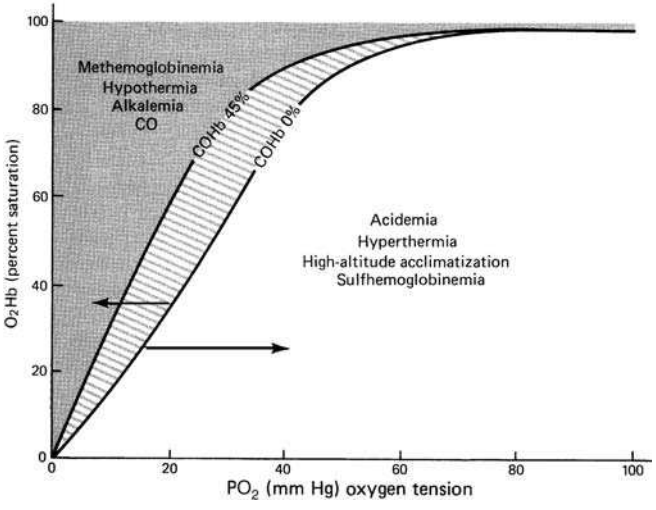

FIG. 22–1. Oxyhemoglobin dissociation curve at 98.6°F (37°C) and pH 7.40. (Hemoglobin does not alter this relationship.)

airway patency is in question, maneuvers to establish and protect the airway, such as repositioning the chin, jaw, or head, suctioning secretions or vomitus, insertion of an oral or nasopharyngeal airway, or insertion of an endotracheal tube, may be required. After the airway is secured, high-flow oxygen should be provided and the depth, rate, and rhythm of respirations evaluated.

Having assured an acceptable airway, the evaluation can proceed. A rapid assessment of the remainder of the vital signs should then occur. Obtaining a history and physical examination, pulse oximetry, arterial blood-gas analysis, measured oxygen saturation, and a chest radiograph are sufficient to determine the diagnosis of pulmonary pathology in most cases. However, adjuncts, such as measurement of negative inspiratory force (NIF), invasive hemodynamic monitoring, evaluation of the arterial–venous oxygen difference, xenon ventilation, and technetium scanning, may be required.

History

A directed history must include questions on the nature, onset, and duration of symptoms; substance use and abuse; home and occupational exposures; and underlying pulmonary pathology. If the patient is suffering from a significant degree of respiratory compromise, most or all of the history may have to be obtained from friends, relatives, paramedics, coworkers, or others.

Physical Examination

The physical evaluation must include a detailed assessment of depth, rate, and rhythm of respirations, use of accessory muscles, direct evaluation of the oropharynx, position of the trachea, and presence and quality of breath sounds. Skin, nail bed, and conjunctival color must be observed for pallor or cyanosis. A general assessment of muscle tone, with a specific emphasis on

ocular and neck muscles, may give clues to flaccidity or rigidity syndromes that interfere with respiration.

Pulse Oximetry

This common technique has gained wide acceptance in medicine. However, some limitations require discussion. Because the oxyhemoglobin saturation curve becomes quite flat above 90% saturation, small changes in saturation greater than 90% may represent very large changes in PO_2. Thus a decrease from 97% saturation to 95% saturation may represent a substantial change in PO_2. Also, if total hemoglobin is low, oxygen-carrying capacity is inadequate even with excellent saturation. Finally dyshemoglobinemias such as carboxyhemoglobin, methemoglobin, and possibly sulfhemoglobin, interfere with the accuracy of pulse oximeter determinations and are of particular concern in the poisoned patient. Because carboxyhemoglobin is falsely interpreted by the pulse oximeter as mostly oxyhemoglobin, readings tend to appear normal even with significant carbon monoxide poisoning. Newer pulse oximeters are able to distinguish carboxyhemoglobin and methemoglobin from oxyhemoglobin and deoxyhemoglobin.

Pulse oximetry is best used as an initial screening tool for hypoxic hypoxia and later in combination with the initial arterial blood-gas measurement, as a determination of the patient's response to therapy.

Blood-Gas Analysis

Arterial blood-gas analysis is an easy and rapid means of evaluating both acid–base status and gas exchange. Because it is easier to obtain, venous blood-gas analysis is often used as a substitute for arterial blood-gas analysis. When compared to arterial values, venous pH and PO_2 are lower, whereas PCO_2 is higher. Errors can be introduced by increased muscle activity of the extremity being tested (eg, seizures) or the prolonged placement of a tourniquet while attempting phlebotomy. Although a venous blood gas is generally acceptable for assessment of acid–base status, it cannot provide a good evaluation of gas exchange. The arterial PO_2 is generally considered adequate only if it lies within the flat portion at the upper right of the sigmoidal-shaped oxyhemoglobin dissociation curve. That portion of the curve includes the PO_2 range from 60 to 100 mm Hg, which corresponds to oxygen saturations greater than 90%.

Significance of a Decreased PO_2

In a patient with a diminished PO_2, five clinically relevant mechanisms for the hypoxemia should be considered: (a) alveolar hypoventilation; (b) V/Q mismatch; (c) shunting; (d) diffusion abnormality; and, rarely, (e) a decrease in inspired FiO_2. In most clinical circumstances, diffusion defects cannot be distinguished from V/Q mismatch. Usually the responsible mechanism can be identified by calculating the alveolar-arterial oxygen (A-a) gradient (see below). In patients with alveolar hypoventilation, the A-a gradient is completely normal (15 mm Hg or less when breathing room air). Patients with V/Q mismatch have an A-a gradient that is increased but normalizes when 100% oxygen is administered for at least 20 minutes. Because the arterial PO_2 on 100% oxygen reaches approximately 575 mm Hg, the normal A-a gradient is less than 100 mm Hg on 100% oxygen. In contrast, a patient with a shunt also has an increased A-a gradient while breathing room air, but when

100% oxygen is administered, the arterial PO_2 will fall substantially below 575 mm Hg and the A-a gradient will not normalize. Finally, in the case of a patient with hypoxia resulting from breathing in an environment in which the FiO_2 is less than 21%, the PO_2 should correct rapidly when the patient is removed from the environment or supplemental oxygen is delivered.

In general, as discussed previously, a low PO_2 can be improved by supplying supplemental oxygen. Although in this instance the patient's laboratory values may be corrected, the underlying process persists. It is important to remember that the laboratory correlate of hypoventilation is hypercapnia on the arterial blood-gas analysis. If hypercapnia is associated with a low arterial pH (less than 7.35), assisted ventilation should be considered, regardless of whether the PO_2 corrects with supplemental oxygen.

Use of the Cooximeter

Routine analysis of an arterial blood-gas yields a measured pH, measured PO_2, and measured PCO_2. Ordinarily, the serum bicarbonate, base excess, and percent oxygen saturation of hemoglobin are all calculated values. Because the oxygen saturation is calculated from the measured PO_2 using the oxyhemoglobin dissociation curve, it represents only the saturation of normal hemoglobin. Thus, in the presence of even a small percentage of abnormal hemoglobin, the calculated oxygen saturation overestimates the total oxygen content of the blood. Cooximeters spectrophotometrically measure total hemoglobin, oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin. The resultant saturation is a measured oxygen saturation of the total hemoglobin by including four common hemoglobin variants, and thus correlates with the total oxygen content of the blood.

The greatest limitation of the cooximeter occurs when dealing with uncommon hemoglobins. Consequently, rare dyshemoglobinemias, such as sulfhemoglobin, are interpreted as one or a combination of the four common hemoglobin variants, giving erroneous results. This phenomenon commonly occurs in neonates, where fetal hemoglobin may be interpreted as carboxyhemoglobin. Some newer cooximeters are unaffected by fetal hemoglobin and can also measure sulfhemoglobin.

Chest Radiography

Radiographic detection of a pneumothorax or pneumomediastinum, cardiogenic pulmonary edema, ALI and ARDS, aspiration pneumonitis, or the presence of a foreign body is crucial, but can usually be delayed until the initial evaluation is completed.

Calculation of the A-a Gradient

The following equation is used to calculate the A-a gradient when the patient is breathing room air:

$$150 \ [PaO_2 + (1.25)\ (PCO_2)]$$

23 Cardiovascular Principles

The maintenance of adequate tissue perfusion depends on the volume status and vascular resistance, cardiac contractility, and cardiac rhythm. These components of the hemodynamic system are all vulnerable to the effects of xenobiotics. Consequently, cardiovascular toxicity may be manifested by the development of (a) hemodynamic instability, (b) heart failure, (c) cardiac conduction abnormalities, or (d) dysrhythmias. The presence of these specific cardiovascular abnormalities may be helpful in determining the type of toxic exposure. Even when multiple cardiovascular abnormalities occur, the specific pattern of the anomalies (toxicologic syndrome) may suggest a particular class or type of xenobiotic.

MECHANISMS OF CARDIOVASCULAR TOXICITY

An alteration in hemodynamic functioning may be caused by either indirect metabolic effects or by direct effects on the nervous system, heart, or blood vessels. Poisoning may lead indirectly to hemodynamic changes secondary to the development of acidemia, alkalemia, hypoxia, or electrolyte abnormalities. In these patients, supportive care with ventilation, oxygenation, and fluid and electrolyte repletion usually improves the cardiovascular status. These cardiovascular abnormalities are a result of metabolic changes and are generally not useful in the identification of a specific ingested xenobiotic.

Xenobiotics also can cause specific hemodynamic abnormalities because of their direct effects on the myocardial cells, the cardiac conduction system, and the arteriolar smooth muscle cells. These effects are frequently mediated by interactions with cellular ion channels or cell membrane receptors. A rational approach to treatment of xenobiotic-induced hemodynamic effects is based on the underlying pharmacology and pathophysiology of the neurohormonal receptors, membrane ion channels, intracellular calcium regulation, and autonomic nervous system.

ION CHANNELS OF THE MYOCARDIAL CELL MEMBRANE

Electrophysiologic studies have identified the functional types of membrane receptors and ion channels.

Potassium Channel

The voltage-sensitive potassium channels are categorized based on their speed of activation and their voltage response. These include the "delayed rectifier" potassium currents, particularly the I_{Kr} (rapidly activating, or HERG [human ether-a-go-go-related gene] channel) and the I_{Ks} (slowly activating) channels.

Sodium Channel

The voltage-responsive sodium channels are responsible for the initiation of depolarization of the myocardial membrane.

Calcium Channel

Calcium channel conductivity across the myocardial cell membrane is critical for appropriate duration of cell membrane depolarization and for initiation of

cellular contraction. The best characterized of the calcium channels are the membrane-bound slow L-type, the fast T-type, and the ryanodine receptor calcium channel in the sarcoplasmic reticulum.

Ion Channels and the Myocardial Cell Action Potential

Figure 5–1 shows the typical action potential of myocardial cell depolarization, the electrolyte fluxes responsible for the action potential, and the resulting ECG complex. The action potentials of the contractile and the conductive cells are depicted.

The action potential is divided into five phases: phase 0, depolarization; phase 1, overshoot; phase 2, plateau; phase 3, repolarization; and phase 4, resting. Phase 0 begins when the cell is excited either by a stimulus from an adjoining cell or by spontaneous depolarization of a pacemaker cell. Selective voltage-gated fast sodium channels (I_{Na+}) open, resulting in rapid depolarization of the membrane. At the end of phase 0, the voltage-sensitive sodium channels close and a transient outward potassium current (I_{TO}) occurs, the latter resulting in a partial repolarization of the membrane.

During phase 2 (plateau phase), the inward depolarizing calcium currents are largely balanced by the outward repolarizing potassium currents. Voltage-sensitive calcium channels open, allowing Ca^{2+} movement down the concentration gradient into the cell. Simultaneously, the outward potassium currents, particularly the I_{Kr} (rapidly activating) and the I_{Ks} (slowly activating) currents, open, gradually increasing in conductance to terminate the plateau phase of the action potential and initiate cellular repolarization (phase 3).

Phase 4 is the resting state for much of the myocardium except the pacemaker cells, and corresponds to diastole in the cardiac cycle. During phases 3 and 4, active transport of Na^+, K^+, and Ca^{2+} against their electrochemical gradients returns the myocyte to the baseline resting state. The immense transmembrane electrochemical gradient is maintained during the resting state by a Ca^{2+}–Na^+ exchange mechanism and by adenosine triphosphate (ATP)-dependent pumps in the membrane that together move Ca^{2+} out of the cells.

During phases 0–2, the cell cannot be depolarized again with another stimulus; the cell is *absolutely refractory*. During the latter half of phase 3, as the calcium channels convert from their inactivated to their resting states, an electrical stimulus of sufficient magnitude may cause another depolarization; the cell is *relatively refractory*. During phase 4, the cell is no longer refractory, and any appropriate stimulus that reaches the threshold level can cause depolarization.

Calcium, Calcium Channels, and Cell Contraction

The contraction and relaxation cycle of the myocyte occurs as calcium entry through L-type channels triggers the flux of Ca^{2+} from the sarcoplasmic reticulum (SR) into the cell cytoplasm. This phenomenon of calcium-induced calcium release results in a rapid increase in the intracellular Ca^{2+} concentration, and initiates rapid myosin and actin interaction. At the conclusion of cellular contraction, an SR-associated adenosine triphosphatase (ATPase) calcium pump returns the cytosolic Ca^{2+} into the SR. Patients poisoned by calcium channel blockers have less Ca^{2+} entry into the cell during cardiac membrane depolarization. Administration of exogenous Ca^{2+} increases the concentration gradient across the cell membrane, enhances flow through available Ca^{2+} channels, and

TABLE 23–1. Xenobiotics That Cause Bradycardia

α_1-Adrenergic agonists (reflex bradycardia)
Phenylephrine
Phenylpropanolamine
α_2-Adrenergic agonists (centrally acting)
Clonidine
Guanfacine
Guanabenz
Methyldopa
Antidysrhythmics
Amiodarone
Sotalol
β-Adrenergic antagonists
Calcium channel blockers
Cardioactive steroids
Cholinergics
Carbamates or organic phosphorus compounds
Edrophonium
Neostigmine
Physostigmine
Opioids
Sedative-hypnotics
Sodium channel openers
Aconitine
Andromedotoxin
Ciguatoxin
Veratridine

restores the triggered response of the RyR2 channels to release Ca^{2+} from the sarcoplasmic reticulum (see Antidotes in Brief: Calcium).

XENOBIOTICS AND BRADYCARDIC DYSRHYTHMIAS

Many xenobiotics (Table 23–1) produce bradycardia. The most profound bradycardia results from overdoses of xenobiotics that have direct depressant effects on the cardiac pacemaker. Heart block and conduction abnormalities may also occur (Table 23–2).

The classes of the antidysrhythmics, their effects on the ion channels and on the action potential, and the resulting ECG abnormalities are shown in Table 23–3 and discussed in detail in Chap. 61.

TACHYCARDIC DYSRHYTHMIAS

Both supraventricular and ventricular tachydysrhythmias can occur in poisoned patients. (Table 23–4). Sinus tachycardia is the most common rhythm disturbance seen in poisoned patients. Parasympatholytic drugs, such as atropine, raise the heart rate to its innate rate by eliminating the inhibitory tonic vagal influence. However, more rapid rates require direct myocardial stimulatory effects generally mediated by β-adrenergic agonism.

DYSRHYTHMIAS ASSOCIATED WITH A PROLONGED QTc INTERVAL: TORSADES DE POINTES

Prolongation of the QT interval corresponds to an increase in the duration of phase 2 or phase 3 of the action potential. The QT interval corresponds to the

TABLE 23–2. Xenobiotics That Cause Conduction Abnormalities and/or Heart Block

α_1-Adrenergic agonists
α_2-Adrenergic agonists
Amantadine
Anesthetics (local)
Antidysrhythmics (class I and III)
Antihistamines
Antimicrobials
Chloroquine and quinine
Macrolides
Quinolones
Antipsychotics
Atypical antipsychotics
Droperidol
Haloperidol
Phenothiazines
β-Adrenergic antagonists
Calcium channel blockers
Carbamazepine
Cardioactive steroids
Cholinergics
Cocaine
Cyclic antidepressants
Cyclobenzaprine
Electrolytes
Potassium
Magnesium
Metal salts
Arsenic
Methadone
Pentamidine
Propoxyphene

duration of the ventricular action potential and should be measured from the beginning of the QRS to the end of the T wave. The QT interval is normally prolonged at slower heart rates and shortens as the heart rate increases. This is especially important as many of the xenobiotics that affect the QT interval also affect the heart rate. A variety of correction formulas have been used to correct for the effects of heart rate on the QT interval, called the QTc.

Ventricular tachycardia, including torsades de pointes, is usually a reentrant-type rhythm that requires an initiating impulse that spreads through the myocardial tissue and a branch point with unequal refractory periods. The presence of a prolonged QT interval on the ECG may indicate the possible existence of conditions within the myocardium that favor these conditions necessary for occurrence of reentry dysrhythmias.

DECREASED CARDIAC CONTRACTILITY AND CONGESTIVE HEART FAILURE

Xenobiotics can reduce cardiac contractility with resulting decrease in cardiac ejection fraction and cardiac output, decrease in blood pressure, and development of congestive heart failure (CHF). Cardiogenic pulmonary edema

TABLE 23–3. Classes of Antidysrhythmics

Class	Pharmacologic Blockade: Sodium Channels	Pharmacologic Blockade: Potassium Channels	Pharmacologic Blockade: Calcium Channels	Prolongation of ECG Intervals: PR	Prolongation of ECG Intervals: QRS	Prolongation of ECG Intervals: QT	Examples
Sodium channel blockers							
IA	++/+++	++	0	±	↑	↑	Disopyramide Procainamide Quinidine
IB	+/++	±	0	±	±	±	Lidocaine Phenytoin Mexiletine Tocainide
IC	+++	++/+++	0	↑	↑	↑↑	Encainide Flecainide Propafenone Moricizine
β-Adrenergic antagonists							
II	0	0	+(indirect)	↑	±	±	Propranolol Atenolol Esmolol Metoprolol Timolol
Potassium channel blockers							
III	+	++	0	↑	±	↑	Amiodarone Bretylium Sotalol Dofetilide Ibutilide[a]
Calcium channel blockers							
IV	0	0	+++	↑	±	±	Verapamil Diltiazem

+ = Mild blockade; + + = moderate blockade; + + + = marked blockade; ↑ = increases; ± = no significant effect.
[a]Ibutilide actually activates a slow inward sodium channel rather than blocking outward potassium currents, but is classified as class III because of its increased action potential duration and atrial and ventricular refractoriness, which are typical of class III agents.

generally occurs as a result of the direct effects of the xenobiotic on the contractility, or inotropy, of the heart, or through increases in the preload or afterload. Acute cardiogenic pulmonary edema, resulting from a decreased cardiac output, occurs primarily in patients poisoned by a calcium channel blocker or β-adrenergic receptor antagonist. Other xenobiotics that can exert direct depressant effects on cardiac contractility include antihistamines, phenothiazines, antidysrhythmics, and anesthetics. Many of these xenobiotics reduce contractility through sodium channel blockade, which, by slowing intraventricular conduction, reduces the ability of the heart to contract efficiently.

THE AUTONOMIC NERVOUS SYSTEM AND HEMODYNAMICS

The hemodynamic effects of many xenobiotics are mediated by changes in the autonomic nervous system. The autonomic nervous system is functionally

TABLE 23–4. Xenobiotics That Cause Ventricular and Supraventricular Tachydysrhythmias

Amantadine
Antidysrhythmics
Anticholinergics
Antihistamines
Botanicals and plants (Chap. 114)
Carbamazepine
Cardioactive steroids
Chloroquine and quinine
Cyclic antidepressants
Cyclobenzaprine
Flumazenil
Hydrocarbons and solvents
Halogenated hydrocarbons
Inhalational anesthetics
Jellyfish venom
Metal salts
Arsenic
Iron
Lithium
Magnesium
Potassium
Pentamidine
Phenothiazines
Phosphodiesterase inhibitors
Amrinone
Methylxanthines
Propoxyphene
Sedative-hypnotics
Chloral hydrate
Ethanol
Sympathomimetics
Catecholamines
Cocaine
Thyroid hormone preparations

divided into the sympathetic (ie, adrenergic) and parasympathetic (ie, cholinergic) systems. These two systems, which share certain common features, function semi-independently of one another. Through complex feedback, the two systems provide the balance needed for existence under changing external conditions.

The sympathetic nervous system is primarily responsible for the maintenance of arteriolar tone and cardiac function. Although the ganglionic neurotransmitter of the sympathetic nervous system is acetylcholine, norepinephrine is its primary postganglionic neurotransmitter (Fig. 23–1). Upon release into the synapse, norepinephrine binds to the postsynaptic adrenergic receptors to elicit an effect by the postsynaptic cell.

Adrenergic Receptors

Activation of these postsynaptic α_2 receptors in the cardiovascular control centers in the medulla and elsewhere in the central nervous system decreases sympathetic outflow from the brain. Therefore, α_2-adrenergic agonists gener-

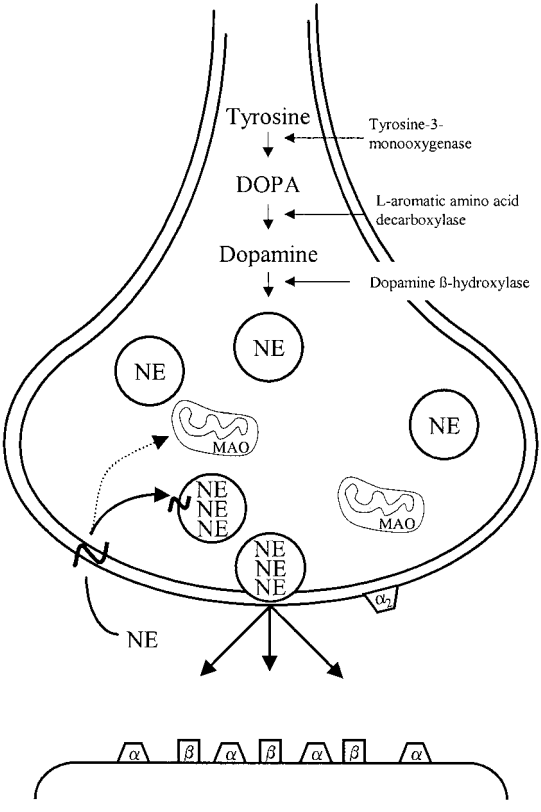

FIG. 23–1. Shown is the synthesis in storage granules, release, reuptake, and degradation of norepinephrine (NE). NE is synthesized in storage vesicles in the nerve ending. These vesicles fuse with the neuronal membrane in response to stimulation and release the NE into the synaptic space. The NE binds postsynaptic adrenergic receptors, after which it either undergoes active reuptake into the proximal neuron or is metabolized. MAO = monoamine oxidase; ~ = reuptake mechanism.

ally cause decreased peripheral vascular resistance, decreased heart rate, and decreased blood pressure (even though some blood vessels have α_2-adrenergic receptors that mediate vasoconstriction). The α_1-adrenergic receptors are located on postsynaptic cells outside the central nervous system, primarily on blood vessels, and mediate arteriole constriction.

The most prevalent β-adrenergic subtype in the heart is β_1, although β_2 and β_3 receptors are also present. Stimulation of the β_1-adrenergic receptors increases heart rate, contractility, conduction velocity, and automaticity. The β_2-adrenergic receptors are primarily responsible for relaxation of smooth muscle with resulting bronchodilation and arteriolar dilation. The β_3 receptors are located primarily on adipocytes where they play a role in lipolysis and thermogenesis.

Cellular Physiology of the Adrenergic Receptors

The effects of adrenergic agents on the cell are primarily mediated through a secondary messenger system of cyclic adenosine monophosphate (cAMP). The intracellular cAMP level is regulated by the membrane interaction of three components: the actual adrenergic receptor, a "G protein" complex, and adenyl cyclase, the enzyme that synthesizes cAMP in the cell (Chap. 14).

HEMODYNAMIC EFFECTS OF XENOBIOTICS

Xenobiotics that act directly on the cardiovascular or nervous system may cause a characteristic alteration of blood pressure, heart rate (ie, chronotropy), and cardiac rhythm. Recognizing these patterns and understanding their etiology allows for specific, rather than empiric, therapy.

Blood Pressure Abnormalities

Blood pressure (BP) is dependent on normal cardiac and vascular function. The blood pressure is directly related to the heart rate (HR), the stroke volume (SV), and the systemic vascular resistance (SVR): BP = HR × SV × SVR. The systolic component of the blood pressure measurement is a reflection of the inotropic state of the myocardium, while the diastolic component reflects the vascular tone. It is important, as described below, to consider both

TABLE 23–5. Xenobiotics That Commonly Cause Hypertension

Hypertensive effects mediated by α-adrenergic receptor interaction	**Hypertensive effects not mediated by α-adrenergic receptor interaction**
Direct α-receptor agonists	β-Adrenergic receptor agonists[b]
Clonidine[a]	Nonselective
Epinephrine	Isoproterenol
Ergotamines	Cholinergics[a]
Methoxamine	Corticosteroids
Norepinephrine	Nicotine[a]
Phenylephrine	Vasopressin
Tetrahydrozoline	
Indirect-acting agonists	
Amphetamines	
Cocaine	
Dexfenfluramine	
Monoamine oxidase inhibitors	
Phencyclidine	
Yohimbine	
Direct- and indirect-acting agonists	
Dopamine	
Ephedrine	
Metaraminol	
Naphazoline	
Oxymetazoline	
Phenylpropanolamine	
Pseudoephedrine	

[a]These may cause transient hypertension followed by hypotension.
[b]These can also cause hypotension.

components of the blood pressure, as the many compensatory mechanisms within the cardiovascular system produce recognizable patterns of blood pressure alteration.

Many xenobiotics affect blood pressure by modulation of the normal chemical interactions at the postganglionic sympathetic neurons. The interaction between these nerve endings and the receptors on vascular and cardiac smooth muscle largely determines the patient's blood pressure. Xenobiotics may initiate complex interactions at this postganglionic neuron that result in hypotension or hypertension.

Hypertension Caused by Xenobiotics

Hypertension may be a result of an increase in either inotropy or vascular resistance or both. For example, stimulation of the α_1-adrenergic receptor causes hypertension through vasoconstriction, and stimulation of the β_1-receptor causes hypertension through enhanced myocardial contractility (Table 23–5).

The pattern of blood pressure elevation may sometimes be helpful in determining the specific class of sympathomimetic ingested. For example, nonselective β-adrenergic agonists (those that agonize at both β_1 and β_2) produce β_1-mediated systolic hypertension (through inotropic effects) with β_2-mediated vascular vasodilation and diastolic hypotension. This results in a wid-

TABLE 23–6. Heart Rate and ECG Abnormalities of Xenobiotics That Cause Hypotension

	Characteristic ECG Abnormalities		
Heart Rate	No Change	Heart Block or Prolonged Intervals	Dysrhythmia
Bradycardia	α_2-Adrenergic agonists Opioids Sedative-hypnotics Vancomycin	β-Adrenergic antagonists Calcium channel blockers Cholinergics Digoxin Magnesium (severe) Propafenone Sotalol	Digoxin Plant toxins Aconitine Andromedotoxin Veratrine Propafenone Propoxyphene Sotalol
Tachycardia	Angiotensin-converting enzyme inhibitors Arterial dilators Belladonna alkaloids Bupropion Cocaine Disulfiram Diuretics Iron Noncyclic anti-depressants Yohimbine	Anticholinergics Antidysrhythmics Antihistamines Cocaine Cyclic antidepres-sants Phenothiazines Quinine/chloroquine	Anticholinergics Antidysrhythmics Antihistamines Arsenic Chloral hydrate Cocaine Cyclic antidepres-sants Methylxanthines Noncyclic antide-pressants Phenothiazines Sympathomimetics

ened pulse pressure, which is the numerical difference between the systolic and diastolic pressures.

Hypotension Caused by Xenobiotics

An extremely large number of xenobiotics are reported to cause hypotension (Table 23–6). However, the hypotension often is not a direct action of the xenobiotic. Rather, the cause of hypotension is coexisting hypoxia, acidosis, anaphylaxis, volume depletion, or dysrhythmias. The terminal event in any patient with massive poisoning may be cardiovascular collapse and hypotension.

Typically, hypotension in adults is arbitrarily defined as a systolic blood pressure of less than 90 mm Hg. However, this is not an adequate clinical parameter. Hypotension is best clinically defined as inadequate tissue perfusion. The clinical assessment of tissue perfusion is based on the vital signs, skin

TABLE 23–7. Xenobiotics That Cause Orthostatic Hypotension

- Antianginals
  - β-Adrenergic antagonists
  - Calcium channel blockers
  - Nitrates
- Antidepressants
  - Cyclic
  - MAO inhibitors
- Antihypertensives
  - Angiotensin-converting enzyme inhibitors
  - Angiotensin receptor antagonists
  - Central α_1-adrenergic agonists
    - Clonidine
    - Guanabenz
    - Guanfacine
    - Methyldopa
- Antiparkinsons
  - Bromocriptine
  - L-Dopa
  - Pergolide mesylate
- Antipsychotics
  - Butyrophenones
  - Phenothiazines
- CNS depressants
  - Ethanol
  - Opioids
  - Sedative-hypnotics
- Diuretics
  - Loop diuretics
  - Thiazides
- Ganglionic blockers
  - Miscellaneous
    - Reserpine
  - Peripheral α-adrenergic antagonists
    - Phenoxybenzamine
    - Prazosin
  - Trimethaphan
- Vasodilators
  - Hydralazine

TABLE 23–8. Clues That an Unanticipated Xenobiotic Might be the Cause of Hemodynamic Compromise or Dysrhythmia

History
New-onset, concomitant seizure
Gastrointestinal disturbances (colicky pain, nausea, vomiting, diarrhea)
Prior ingestion of medications (consider possibility that the container is mislabeled or misidentified)
Depression (even if patient denies ingestion)
Suspected myocardial ischemia in patient younger than 35 years old
Past medical history
Treatment with any cardiac medications (especially antidysrhythmics or digoxin)
History of psychiatric illness, asthma, or hypertension
History of drug use or abuse
Physical examination and vital signs
Heart rate
Sinus tachycardia with rate >130 beats/min
Sinus tachycardia without apparent identified cause
Sinus bradycardia
Respiratory rate
Any unexplained depression or elevation in rate
Temperature
Elevation especially if >106°F (>41.1°C)
Hypothermia
Dissociation between typically paired changes, for example:
Hypotension and bradycardia (tachycardia expected)
Fever and dry skin (diaphoresis expected)
Hypertension and tachycardia (reflex bradycardia anticipated)
Depressed mental status and tachypnea (decreased respirations common)
Relatively rapid changes in vital signs
Initial hypertension becomes hypotension
Increasing sinus tachycardia or hypertension
General
Alteration in consciousness, such as depressed mental status, confusion, or agitation
Findings usually not associated with cardiovascular diseases
Ataxia, bullae, dry mucous membranes, lacrimation, miosis or mydriasis, nystagmus, unusual odor, flushed skin, salivation, tinnitus, tremor, visual disturbances
Findings consistent with a toxic syndrome
Especially findings consistent with anticholinergics, sympathomimetics, or sedative-hypnotics
Laboratory tests
Any unexpected or unexplained laboratory result, especially:
Metabolic acidosis
Respiratory alkalosis
Hypokalemia or hyperkalemia

color, capillary refill, mental status, urine output and concentration, and acid–base balance. However, if a toxin directly affects one or more of these clinical parameters, the clinical assessment of volume and hemodynamic status may be difficult. Measurement of central venous pressure is beneficial in the early treatment of the sepsis syndrome and would most likely be beneficial in decision making for hypotension of other etiologies, including that occurring in poisoned patients. Cardiac filling pressure, cardiac output, systemic vascular resistance, and precise arterial pressures may be necessary in critically ill patients following consequential xenobiotic exposures.

Poor tissue perfusion may result from hypovolemia, decreased peripheral vascular resistance, myocardial depression, or a dysrhythmia that reduces the cardiac output. A single xenobiotic may exert several effects on the hemodynamic system. Appropriate treatment of the hypotension requires an understanding of the pathophysiologic consequences of the xenobiotic and the resultant hemodynamic derangement.

Assessment of Volume Status in the Poisoned Patient

Assessment of volume status may be particularly difficult in the poisoned patient because of functional alterations in the autonomic nervous systems and pharmacologic effects of the xenobiotic. For example, the usual signs of dehydration, such as dry mucous membranes, dry skin, low blood pressure, tachycardia, narrowed pulse pressure, clouded sensorium, and decreased urine output, can be mimicked by a number of xenobiotics, including tricyclic antidepressants. In most cases, information about the adequacy of the patient's volume status may be obtained by orthostatic vital sign testing. Even with a 30% or greater volume loss, the supine blood pressure may remain normal in young, previously healthy patients. Normally, the cardiovascular system responds to sitting or standing with vasoconstriction and a slight increase in heart rate. Patients with hypovolemia will be unable to maintain adequate intravascular pressure when upright and will have either an exaggerated reflex increase in heart rate or a drop in blood pressure (ie, orthostasis) (Table 23–7).

A variety of clinical clues, when present, should heighten the physician's suspicion that a xenobiotic may be responsible for the hemodynamic compromise or dysrhythmia. Table 23–8 lists some of these clues.

24 | Hematologic Principles

Blood delivers oxygen and other essential substances throughout the body, removes waste products of metabolism, transports hormones, signals and defends against infection, promotes healing via the inflammatory response, and maintains the vascular integrity. It also contains the central compartment of classical pharmacokinetics, and thereby comes into direct contact with virtually every toxin. In addition to transporting xenobiotics throughout the body, blood and the blood-forming organs can be directly affected by these same xenobiotics. Both dose-dependent and idiosyncratic reactions are common.

HEMATOPOIESIS

Hematopoiesis is the development of the cellular elements of blood. The majority of the cells of the blood system may be classified as either lymphoid (B, T, and natural-killer lymphocytes) or myeloid (erythrocytes, megakaryocytes, granulocytes, and macrophages). All of these cells are descended from *hematopoietic stem cells*.

Bone Marrow

Fetal erythropoiesis moves from the liver to the marrow by the end of the last trimester. The arterial supply of the bone marrow comes from nutrient arteries. Blood from these two systems mix and enter the marrow sinus system, which drains into the systemic circulation.

The extracellular matrix provides a structural network to which the progenitors are anchored. Hematopoietic progenitor cells have receptors that bind to particular matrix molecules. As the cells approach maturity, they lose their surface receptors, presumptively allowing them to leave the hematopoietic space and enter the venous sinuses. Blood cell release depends on the development of a pressure gradient that drives mature cells through channels in endothelial cell cytoplasm. Pressure within the marrow is increased by erythropoietin and by granulocyte colony-stimulating factor (GCSF).

A stem cell is capable of self-renewal as well as differentiating into a specific cell type. The pluripotent hematopoietic stem cell can continuously replicate, while awaiting the appropriate signal to differentiate into either a myeloid stem cell (for myelo-, erythro-, mono-, or megakaryopoiesis) or a lymphoid stem cell (for lymphopoiesis of T, B, null, and natural-killer cells).

Cytokines are soluble mediators secreted by cells for cell-to-cell communication. Cytokines promote or inhibit the differentiation, proliferation, and trafficking of blood cells and their precursors. They include growth factors or colony-stimulating factors (CSFs), interleukins, monokines, interferons, and chemokines. Recombinant cytokines are being developed for therapeutic use in immunocompromised patients, transplant recipients, sepsis, and cancer. They have also been used in clinical toxicology for the treatment of colchicine and podophyllum toxicity.

With the use of monoclonal antibody technology, cell surface antigens can be identified and are used increasingly to characterize cell types. The cluster designation (CD) nomenclature is used, and more than 160 types have been classified.

Aplastic Anemia

Aplastic anemia is characterized by pancytopenia on peripheral smear, a hypocellular marrow, and delayed plasma iron clearance. Severe aplastic anemia denotes a granulocyte count of less than 500 cells/mm^3, platelets of less than 20,000/mm^3, and a reticulocyte count of less than 1% after correction for anemia. Following acute insult and depletion of extracirculatory reserves, cell line counts fall at a rate inversely proportional to their life span: granulocytes (half-life: 6–12 hours in the circulation) disappear within days, platelets (life span: 7–10 days) decline by half in about 5 days, erythrocytes (normal life span: 120 days) take up to 2 months before being reduced to 50% of their baseline counts. Specific etiologies of acquired aplastic anemia include certain xenobiotics (Table 24–1). The mechanism is believed to involve the acquired defects of the hematopoietic stem cells, and abnormal humoral and cellular immune control of hematopoiesis. It is now believed that the majority of cases of aplastic anemia previously determined to be idiosyncratic are caused by immunologically mediated tissue-specific destruction of CD34+ hematopoietic progenitor cells. Following an exposure to an inciting antigen, T cells and cytokines act destructively on stem cells, reducing their numbers so that normal levels of circulating mature leukocytes, erythrocytes, and platelets fall to dangerously low levels. Human leukocyte antigen (HLA) DR2 is overrepresented among European and American patients with aplastic anemia. Clozapine-induced agranulo-

TABLE 24–1. Xenobiotics Associated with Aplastic Anemia

Analgesics	Antipsychotics
Acetaminophen	Chlorpromazine
Acetylsalicylic acid	Clozapine
Diclofenac	Antirheumatics
Dipyrone	Gold salts
Indomethacin	Methotrexate
Phenylbutazone	D-Penicillamine
Antibiotics	Antithyroids
Azidothymidine	Propylthiouracil
Chloramphenicol	Diuretics
Daunorubicin[a]	Acetazolamide
Doxorubicin[a]	Metolazone
Mefloquine	Occupational
Penicillin	Arsenic[a]
Anticonvulsants	Benzene[a]
Carbamazepine	Cadmium
Felbamate	Copper
Antidysrhythmics	Pesticides
Tocainide	Antineoplastics[a]
Antihistamines	Antimetabolites
Cimetidine	Colchicine
Antiplatelets	Mustards
Ticlopidine	Vinblastine
	Vincristine
	Radiation[a]

[a]Denotes xenobiotics that predictably result in bone marrow aplasia following a sufficiently large exposure.

cytosis is associated with the HLA B38, DR4, and DQ3 haplotypes, underlining a genetic predisposition to acquired aplastic anemia.

THE ERYTHRON

The erythron can be considered to be a single tissue, defined as the entire mass of erythroid cells beginning with the first committed progenitor cell and ending with the mature circulating erythrocyte. The primary function of the erythron is to transport molecular oxygen throughout the organism.

Erythropoietin

Erythropoietin (EPO) is a glycoprotein hormone of molecular weight 34,000 daltons that is produced in the epithelial cells lining the peritubular capillaries in the normal kidney. Anemia and hypoxemia stimulate its synthesis. EPO promotes erythroid differentiation, the mobilization of marrow progenitor cells, and the premature release of marrow reticulocytes.

The Mature Erythrocyte

The mature erythrocyte (red blood cell) is a highly specialized cell, designed primarily for oxygen transport. Accordingly, it is densely packed with hemoglobin, which constitutes approximately 90% of the dry weight of the erythrocyte, or 30–35 g/dL. During maturation, the erythrocyte loses its nucleus, mitochondria, and other organelles, rendering it incapable of synthesizing new protein, replicating, or using the oxygen being transported for oxidative phosphorylation.

Metabolism

Without mitochondria and the ability to efficiently generate adenosine triphosphate (ATP) using molecular oxygen, the mature erythrocyte has a severely limited repertoire of intermediary metabolism compared to most mammalian cells. The Embden-Meyerhof pathway for glycolysis is the only source of ATP for the erythrocyte and accounts for approximately 90% of the glucose imported by the cell. During glycolysis, metabolism can be diverted into the Rapoport-Luebering shunt, generating 2,3-bisphosphoglycerate (2,3-BPG, formerly known as 2,3-diphosphoglycerate or 2,3-DPG) in lieu of ATP. As an alternative to glycolysis, glucose can be directed toward the hexose monophosphate shunt during times of oxidant stress. This pathway results in the generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which the erythrocyte uses to maintain reduced glutathione. The initial, rate-limiting step of this pathway is controlled by glucose-6-phosphate dehydrogenase (G6PD). Accordingly, cells deficient in this enzyme are less able to maintain glutathione in a reduced state and are vulnerable to oxidant stress.

Hemoglobin

Hemoglobin, the major constituent of the cytoplasm of the erythrocyte, is a conjugated protein with a molecular weight of 64,500 daltons. One molecule is composed of 4 protein or globin chains, each attached to a prosthetic group called *heme*. Heme contains an iron molecule complexed at the center of a porphyrin ring. Hemoglobin is so efficient at binding and carrying oxygen that it enables blood to transport 100 times as much oxygen as could be carried by plasma alone (Chap. 22).

Heme Synthesis

Heme is the iron complex of protoporphyrin IX. The first step in the synthesis of heme takes place in the mitochondrion and is the condensation of glycine and succinyl coenzyme A (CoA) to form δ-aminolevulinic acid (δ-ALA). Xenobiotics that increase the rate of synthesis of δ-ALA may precipitate an inducible porphyric crisis. The next step in the synthesis of hemoglobin is the formation of the porphobilinogen via the condensation of 2 molecules of ALA. This reaction is catalyzed by ALA dehydratase and is inhibited by lead. Figure 24–1 depicts these and subsequent steps. Most steps in the heme biosynthetic pathway are inhibited by lead. ALA dehydratase is the most sensitive, followed by ferrochelatase, coproporphyrinogen decarboxylase, and PBG deaminase.

Oxygen–Carbon Dioxide Exchange

The circulatory system allows delivery of oxygen and removal of carbon dioxide throughout the organism. Hemoglobin plays an essential role in the transport and exchange of both gases.

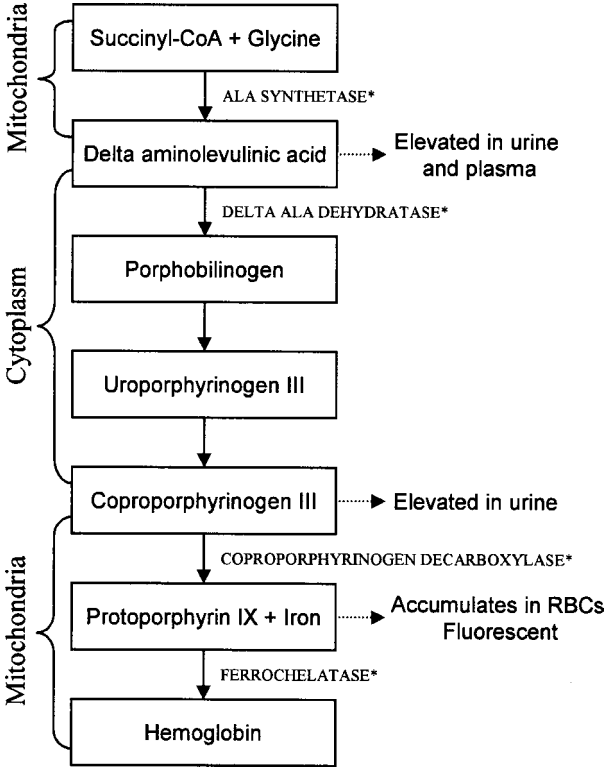

FIG. 24–1. The heme synthesis pathway. The enzymatic steps inhibited by lead are marked with an asterisk (*). RBCs = red blood cells.

The binding of oxygen to each of the 4 iron molecules in heme results in conformational changes that affect binding of oxygen at the remaining sites. This phenomenon is known as cooperativity and is a fundamental property to enable both the transport of relatively large quantities of oxygen and the unloading of most of this oxygen at tissue sites. Cooperativity results from the intramolecular interactions of the tetrameric hemoglobin and is expressed in the sigmoidal shape of the oxyhemoglobin dissociation curve (Chap. 22).

The ability of hemoglobin to buffer the acid equivalent of CO_2 in solution is equally vital to respiratory physiology, as it allows the removal of large quantities of CO_2 from metabolically active tissues with minimal changes in blood pH. Hemoglobin is the largest buffer in circulation, accounting for nearly 7 times the buffer capacity of the serum proteins combined (28 vs. 4 mEq H^+/L of whole blood). Carbon dioxide dissolves into serum and is slowly hydrated to carbonic acid, which dissociates to H^+ and HCO_3^- (pK_a 6.35). The hydration reaction is accelerated from about 40 seconds to 10 milliseconds by the abundant enzyme carbonic anhydrase, which is located within the erythrocyte. Most carbon dioxide collected at the tissues diffuses into erythrocytes, where it becomes H^+ and HCO_3^-. This HCO_3^- is then rapidly transported back to the serum in exchange for chloride. The hydrogen ion is accepted by hemoglobin, largely at the imidazole ring of histidine residues, which have a pK_a of about 7.0. Because deoxyhemoglobin is better able to buffer hydrogen ions, the release of oxygen from hemoglobin at the tissues facilitates the uptake of carbon dioxide into venous blood. Several alterations of the hemoglobin molecule are encountered in clinical toxicology. A detailed discussion of these abnormal hemoglobins appears elsewhere (Chaps. 120 and 122).

Oxidation of the Globin Chain

Oxidation can take place at amino acid side chains of the globin protein. In particular, sulfhydryl groups can oxidize to form disulfide links between cysteine residues, which leads to the unfolding of the protein chain, exposure of other side chains, and further oxidation. When these disulfide links join adjacent hemoglobin molecules, they cause the precipitation of the concentrated hemoglobin molecules out of solution. Eventually, aggregates of denatured and insoluble protein are visible on light microscopy as Heinz bodies. The distortion of the cellular architecture, in particular the loss of fluidity, is a signal to reticuloendothelial macrophages to excise sections of erythrocyte membrane or the entire erythrocyte. To guard against these oxidation reactions, the erythrocyte maintains a pool of reduced glutathione via the actions of the NADPH generated in the hexose monophosphate shunt (assuming adequate G6PD activity to initiate this pathway). This glutathione transfers electrons to break open disulfide links and to preserve sulfhydryl groups in their reduced state.

Hemolysis

Hemolysis is merely the acceleration of the normal process by which senescent or compromised erythrocytes are removed from the circulation. The normal life span of a circulating erythrocyte is approximately 120 days, and any reduction in this life span represents some degree of hemolysis. Table 24–2 presents a brief classification of acquired causes of hemolysis relevant to toxicology. A number of xenobiotics or their reactive metabolites can cause hemolysis via oxidant injury; Table 24–3 provides a partial list.

TABLE 24–2. Xenobiotics Causing Acquired Hemolysis

Immune-mediated
Type I: Drug–red cell complex; IgG triggers complement
Type II: Immune complex–mediated; IgM triggers complement
Type III: True autoimmune response to red cell membrane
Nonimmune-mediated
Oxidants (see Table 24–3)
Nonoxidants
Arsine (AsH_3)
Copper
Lead
Pyrogallic acid
Stibine (SbH_3)
Microangiopathic (eg, ticlopidine, clopidogrel, cyclosporine, tacrolimus)
Venoms (snake, spider)
Osmotic agents (eg, water)
Hypophosphatemia

Immune-Mediated Hemolytic Anemia

The immune-mediated hemolytic anemias occur when ingested xenobiotics trigger an antigen antibody reaction (Table 24–2). The first class of reactions (hapten model) occurs when the xenobiotic acts as a hapten and binds to cell membrane glycoproteins on the surface of the erythrocyte. This results in the formation of a neoantigen, against which IgG develops, and subsequent removal of the erythrocyte by splenic macrophages. The second class of reactions (immune complex) occurs with drugs that have a low affinity for cellular membrane glycoproteins. Small doses of xenobiotics result in hemolysis, and erythrocyte injury is primarily mediated by complement. Complexes of drug and IgM are implicated as the complement trigger in this second pro-

TABLE 24–3. Selected Xenobiotics Causing Oxidative Hemolysis in Normal Host

p-Aminosalicylic acid
Aniline
Benzocaine
Chlorates
Cresol
Dapsone
Hydrogen peroxide
Hydroxylamine
Isobutyl nitrite
Methylene blue
Naphthalene
Nitrites
Nitrofurantoin
Oxygen
Phenacetin
Phenazopyridine
Phenol
Platinum salts
Sulfonamides

cess. The third class of reactions (true autoimmune) occurs when the xenobiotic alters the natural suppressor system, allowing the formation of antibody to cellular components.

Glucose-6-Phosphate Dehydrogenase Deficiencies

G6PD is the enzyme that catalyzes the first step of the hexose monophosphate shunt: the conversion of glucose-6-phosphate to phosphogluconolactone. In the process, $NADP^+$ is reduced to NADPH, which the erythrocyte uses to maintain a supply of reduced glutathione and to defend against oxidation. It follows that erythrocytes deficient in G6PD activity are less able to resist oxidant attack and, in particular, less able to maintain sulfhydryl groups of hemoglobin in their reduced state, resulting in hemolysis. The term *G6PD deficiency* encompasses a wide range of differences in enzyme activities among individuals. The gene that encodes for G6PD resides near the end of the long arm of the X chromosome. Most mutations consist of a single amino acid substitution, as complete absence of this enzyme is lethal. Although males hemizygous for a deficient gene are more severely affected, females randomly inactivate one X chromosome during cellular differentiation, according to the Lyon hypothesis. Thus female carriers heterozygous for a deficient G6PD gene have a mosaic of erythrocytes, some proportion of which expressed the deficient gene during maturation.

Normal G6PD has a half-life of about 60 days. Because the erythrocyte cannot synthesize new protein, the activity of G6PD normally declines by approximately 75% over its 120-day life span. The World Health Organization classification of G6PD is based on the degree of enzyme deficiency and severity of hemolysis. Both class I and class II patients are severely deficient, with less than 10% of normal G6PD activity. Class I individuals are prone to chronic hemolytic anemia, whereas class II patients experience intermittent hemolytic crises. Class III patients have only moderate (10–60%) enzyme deficiency, and experience self-limiting hemolysis in response to certain drugs and infections. Approximately 11% of African Americans in the United States have a class III deficiency traditionally termed type A, and experience a decline of no more than 30% of the red blood cell mass during any single hemolytic episode. The Mediterranean type found in Sardinia, Corsica, Greece, the Middle East, and India is a class II deficiency, and hemolysis can occur spontaneously or in response to oxidants.

The most common clinical presentation of previously unrecognized G6PD deficiency is the acute hemolytic crisis. Typically, hemolysis begins one to four days following the exposure to an offending xenobiotic (Table 24–4). A decrease in the concentration of hemoglobin occurs. The peripheral smear demonstrates cell fragments and cells that have had Heinz bodies excised. Bone marrow stimulation results in a reticulocytosis by day 5 and an increased erythrocyte mass. In general, a normal bone marrow can compensate for ongoing hemolysis, and can return the hemoglobin concentration to normal. Most crises are self-limiting as a result of the higher G6PD activity of younger erythrocytes.

Megaloblastic Anemia

Vitamins B_{12} and folate are essential for DNA synthesis. A deficiency of vitamin B_{12} or folate may result from nutritional factors, or the use of the folate antagonists methotrexate, pyrimethamine, proguanil, and trimethoprim-sulfa-

TABLE 24–4. Xenobiotics That Can Cause Hemolysis in Patients with Class I, II, or III G6PD Deficiency

Doxorubicin	Phenylhydrazine
Furazolidone	Primaquine
Isobutyl nitrite	Sulfacetamide
Methylene blue	Sulfamethoxazole
Nalidixic acid	Sulfanilamide
Naphthalene	Sulfapyridine
Nitrofurantoin	Toluidine blue
Phenazopyridine	Trinitrotoluene

Adapted from Beutler E: Glucose-6-phosphate dehydrogenase deficiency. N Engl J Med 1991;324:169–174, and Beutler E: G6PD deficiency. Blood 1994;84:3613–3636.

methoxazole. Vitamin B_{12} metabolism can be affected by chronic exposure to nitrous oxide, biguanides, colchicine, and neomycin. Purine analogs (eg, azathioprine, 6-mercaptopurine, 6-thioguanine, acyclovir) and pyrimidine analogs (eg, 5-fluorouracil, 5-azacitidine, zidovudine) can also disrupt nucleic acid synthesis. Chronic ethanol abuse can result in a macrocytic anemia, with increased size of circulating erythrocytes.

Pure Red Cell Aplasia

Pure red cell aplasia is a rare condition in which erythrocyte precursors are absent from an otherwise normal bone marrow. It results in a normocytic anemia with inappropriately low reticulocyte count. Drugs (eg, phenytoin, azathioprine, and isoniazid) cause less than 5% of cases of this uncommon condition.

Erythrocytosis

Erythrocytosis denotes an increase in the red cell mass, either in absolute terms or relative to a reduced plasma volume. An increasingly recognized cause of drug-induced absolute erythrocytosis is the abuse of recombinant human erythropoietin by athletes to enhance aerobic capacity. Cobalt can cause a secondary erythrocytosis by inhibiting oxidative phosphorylation (histotoxic anoxia), and was considered at one time for the treatment of chronic anemia.

THE LEUKON

The leukon represents all leukocytes (white blood cells), including precursor cells, cells in the circulation, and the large number of extravascular cells. They include the granulocytes (neutrophils, eosinophils, and basophils), lymphocytes, and monocytes. Neutrophils (polymorphonuclear leukocytes) are highly specialized mediators of the inflammatory response and are a primary focus of concern regarding hematologic toxicity of xenobiotics. B and T lymphocytes are involved in antibody production and cell-mediated immunity. Monocytes migrate out of the vascular compartment to become tissue macrophages, and regulate immune system function.

Neutropenia and Agranulocytosis

Neutropenia is a reduction in circulating neutrophils at least 2 standard deviations below the age norm. Severe neutropenia is termed *agranulocytosis*, and is gener-

TABLE 24–5. Selected Causes of Idiosyncratic Drug-Induced Agranulocytosis

Anticonvulsants	Antipsychotics
Carbamazepine	Clozapine
Phenytoin	Phenothiazines
Antiinflammatory agents	Antithyroid agents
Aminopyrine	Methimazole
Ibuprofen	Propylthiouracil
Indomethacin	Cardiovascular agents
Phenylbutazone	Hydralazine
Antimicrobials	Lidocaine
β-Lactams	Procainamide
Cephalosporins	Quinidine
Chloramphenicol	Ticlopidine
Dapsone	Vesnarinone
Ganciclovir	Diuretics
Isoniazid	Acetazolamide
Rifampicin	Hydrochlorothiazide
Sulfonamides	Hypoglycemics
Vancomycin	Chlorpropamide
Antirheumatics	Tolbutamide
Gold	Sedative-hypnotics
Levamisole	Barbiturates
Penicillamine	Flurazepam

ally defined as an absolute neutrophil count of less than 0.5×10^9/L. Neutropenia can result from decreased production, increased destruction, or retention of neutrophils in the various storage pools. Their high rate of turnover renders neutrophils vulnerable to any xenobiotic that inhibits cellular reproduction. As such, the various antineoplastic xenobiotics, including antimetabolites, alkylating agents, and antimitotics, predictably cause neutropenia. In contrast, a number of xenobiotics are implicated in idiosyncratic agranulocytosis (Table 24–5).

Eosinophilia

Eosinophilia is arbitrarily classified as mild (absolute eosinophil counts of 0.35–1.5×10^9/L), moderate ($1.5–5 \times 10^9$/L), or severe ($>5 \times 10^9$/L). Allergic or inflammatory reactions, infections with parasites, and certain malignancies, such as lymphoma, are the most common causes of eosinophilia. Two unusual toxicologic outbreaks were characterized by eosinophilia: the Spanish toxic oil syndrome and the eosinophilia-myalgia syndrome (see Chap. 2).

Leukemia

The leukemias represent the malignant, unregulated proliferation of hematopoietic cells. Although monoclonal in origin, they affect all cell lines derived from the progenitor cell. Acute myeloid leukemia (AML) and the myelodysplastic syndromes are the most common leukemias associated with xenobiotics. For example, an association between AML and occupational benzene exposure, radiation, or treatment with alkylating antineoplastic agents is well described. In many cases the latency period between exposure and illness is prolonged.

HEMOSTASIS

In the absence of pathology, blood remains in a liquid, flowing form with cells in suspension. In response to injury, the processes of coagulation and thrombosis are

TABLE 24–6. Xenobiotics Reported to Cause Thrombocytopenia as a Result of Antiplatelet Antibodies[a]

Abciximab	Indinavir
Acetaminophen	Levamisole
Aminoglutethimide	Meclofenamic acid
Aminosalicylic acid	Methyldopa
Amiodarone	Nalidixic acid
Amphotericin B	Oxprenolol
Carbamazepine	Procainamide
Cimetidine	Quinidine
Danazol	Quinine
Diclofenac	Rifampin
Digoxin	Tirofiban
Eptifibatide	Trimethoprim-sulfamethoxazole
Gold	Vancomycin
Heparin	

[a]Xenobiotics reported in at least 2 cases to have definitely caused immune thrombocytopenia, or in at least 5 cases to have probably caused immune thrombocytopenia following therapeutic use.
Adapted from George JN, Raskob GE, Shah SR, et al: Drug-induced thrombocytopenia: A systematic review of published case reports. Ann Intern Med 1998;129:886–890; Rizvi MA, Kojouri K, George JN: Drug-induced thrombocytopenia: An updated systematic review. Ann Intern Med 2001;134:346; and WHO Working Group. Glucose-6-phosphate dehydrogenase deficiency. Bull WHO 1989;67:601–611.

triggered. Coagulation involves complex interactions between vascular endothelium, platelets, and coagulation and fibrinolytic factors. Chapters 57 and 117 discuss coagulation and anticoagulants. Platelet dysfunction commonly occurs with therapeutic doses of aspirin, NSAIDs, cyclooxygenase (COX)-2 inhibitors, glycoprotein IIb/IIIa inhibitors, and thienopyridines. Multiple xenobiotics are reported to cause thrombocytopenia, which is generally mediated via the formation of drug-dependent antiplatelet antibodies (Table 24–6).

25 Gastrointestinal Principles

The gastrointestinal (GI) mucosa, like other mucous membranes, occupies a discrete anatomic niche: the interface between a sterile internal environment and a contaminated external, or luminal environment. Humans are continuously in contact with potential toxins, and the GI mucosa forms part of the initial line of defense. The GI tract may be exposed to a wide variety of potentially toxic xenobiotics, including those with diffuse, nonspecific pathogenic effects, such as caustics and ionizing radiation, as well as highly specific xenobiotics and microbial pathogens. The GI tract, including the liver and pancreas, may be targeted specifically by xenobiotics.

ANATOMIC PRINCIPLES

The luminal GI tract can be divided into five distinct structures and luminal environments: oral cavity and hypopharynx, esophagus, stomach, small intestine, and colon. These environments differ in luminal pH, specific epithelial cell receptors, and endogenous flora. The transitional areas between these distinct organs have specialized epithelia and muscular sphincters, with specific functions and vulnerabilities. The functions of the pancreas and liver are closely integrated with those of the luminal organs, although they are not within the nutrient stream. The liver and its metabolic functions are discussed extensively in Chaps. 13 and 26.

The major structural adaptations of the intestine are designed to increase the surface area available for absorption. Because of the villi and other folds, the surface area of the intestine is 600-fold greater than that of a simple tube. Intestinal epithelium is one of the most rapidly proliferating cell compartments in the body, which makes it vulnerable to xenobiotics that affect the cell cycle.

The most specialized cell type in the intestine is the epithelial cell. There is a polarity, distinct to epithelia, in which one side of the cell (basal) faces "self," while the other side (apical) faces "non-self." To adapt to these different environments and to facilitate the different functions, the apical and basal membranes of the epithelial cell contain different receptors and other surface molecules.

An elaborate system has evolved to protect the GI tract from pathogens, which is part of a common mucosal immune system. Mucosal immunity can be divided into an afferent limb, which recognizes a pathogen and induces the proliferation and differentiation of immunocompetent cells, and an efferent limb, which coordinates and affects the immune response.

The function of the muscle layers is integrated with the enteric nervous system to provide for a coordinated movement of luminal contents through the GI tract so as to maximize absorption, as well as to minimize bacterial growth. For unidirectional flow to occur, the intestine distal to the contraction of circular muscle must decrease its muscular tone and increase compliance, while the intestine proximal to the contraction must increase muscle tone and decrease compliance.

Osmoreceptors and chemoreceptors in the GI tract fine-tune the digestive and absorptive process by regulating transit and secretion, using a variety of neurocrine, paracrine, and endocrine mechanisms, allowing optimum absorp-

tion under a variety of circumstances. For example, hyperosmolar solutions empty more slowly from the stomach than isosmolar solutions. In general, parasympathetic impulses are promotility while sympathetic impulses inhibit motility. Other transmitters, such as serotonin, promote transit, while dopamine and enkephalins slow transit.

The luminal contents also can be considered an anatomic structure, especially the endogenous flora. Microbes within the bulk luminal contents perform biotransforming functions. Other organisms bind to specific receptors in the mucous layer overlying the epithelial cells and may affect epithelial cell gene expression. The importance of the endogenous flora is best illustrated by the result of their unintentional eradication during antibiotic therapy, when the pathogenic or toxigenic bacteria that replace them cause functional alterations and clinical symptoms. Differences in the luminal environment in young infants, compared to adults, allow production of botulinum toxin, with the clinical consequence being infant botulism.

PHYSIOLOGIC PRINCIPLES

Intestinal Absorption

The microenvironment between the bulk luminal contents and the epithelial cells has special properties. An "unstirred layer" is characteristic of all tubular structures through which fluids flow. While the bulk luminal contents move through the GI tract with a velocity that is dependent primarily on muscle activity, water molecules immediately adjacent to the epithelial cell membrane do not move at all, and water molecules slightly more distant from the epithelial cell may move with a velocity below that of the bulk luminal contents. In the stomach, secretion of bicarbonate into the unstirred layer below a mucus layer protects the epithelial cells from gastric acid (pH $\cong$ 1). The chemical composition of the unstirred layer also may differ from that of the bulk luminal contents, resulting in a pH immediately adjacent to the epithelial cell that is lower than the pH of the bulk luminal contents. Based on the absorption rates of weak acids (see below), an acidic microenvironment is hypothesized to face the small intestinal epithelium.

The major barrier to the penetration of xenobiotics and microbes is the GI epithelium, a single-cell–thick membrane. The epithelial cells are attached to one another by structures known as tight junctions, which allow passage only of water, ions, and low molecular weight materials.

The pH of the luminal contents is important in modulating the absorption of acids and bases. Many xenobiotic are either weak acids or weak bases, and the effect of ambient pH is to affect water versus lipid solubility. For example, acids are ionized at basic pH, but nonionized at acid pH. Consequently, weak acids are better absorbed in the stomach and weak bases are better absorbed in the small intestine. This may not always be the case, as the surface area is much greater in the intestine than in the stomach.

XENOBIOTIC METABOLISM

While the liver is usually identified as the site of xenobiotic metabolism, similar functions also are found in the luminal GI tract. The stomach has long been known to contain alcohol dehydrogenase activity. Biotransformation is a property both of luminal bacteria and enterocytes. Metabolism by the intestine affects the amount of orally administered drug that enters the body and contributes to the

TABLE 25–1. Toxic Effects on the Lips, Mouth, and Oropharynx

Type of Effect	Mechanism	Example
Gingivitis, stomatitis (loose teeth)	Inflammation and irritation	Antineoplastics Caustics Ciguatera (tooth pain) Ionizing radiation Metals (arsenic trioxide, mercuric chloride, lead, thallium, zinc chloride) Oxalates Phenol Phenytoin Phosphorus
Edema	Allergic	Penicillin
	Angioedema	Angiotensin-converting enzyme inhibitors
	Mechanical irritation and injury	Caustics Oxalate-containing plants
Pain and ulceration	Early	Caustics Paraquat
	Delayed	Clozapine Antineoplastics
Drooling	Increased saliva	Aminopyridine Cholinergics Nicotine Phencyclidine
	Dysphagia	Foreign bodies (drug packets, batteries)
Dry mouth	Decreased saliva	
	Direct	Anticholinergics Botulism
	From hypovolemia	
	Diuresis	Diuretics Lithium
	Insensible loss	Salicylates CNS stimulants
	Decreased fluid intake	CNS depressants
	Increased GI fluid losses	Cathartics Colchicine
Tongue discoloration	Direct toxic effects	Blue—methylene blue Brown—bromide, bismuth Green—vanadium

first-pass effect, or presystemic disposition. Variations in intestinal metabolism also can influence the pharmacokinetics of a xenobiotic. Metabolism can result in detoxification or the production of toxins, and the rate of metabolism affects the exposure to xenobiotics by the body as a whole and the epithelial cell.

AN ANATOMIC APPROACH TO XENOBIOTICS AND THE GI TRACT

An anatomic approach to the effects of xenobiotics on the lips, mouth, and oropharynx (Table 25–1), the esophagus (Table 25–2), the stomach (Table

TABLE 25–2. Xenobiotics That Affect the Esophagus

Type of Effect	Mechanism	Examples
Pain—retrosternal	Pain fiber stimulation	Alcohol Caustics
	Increased muscle tension caused by	
	Obstruction	Foreign body/drug packets
	Spasm	Caustics
	Mediastinitis/esophageal perforation	Caustics Emetics Foreign body
Dysphagia/odynophagia	Neuromuscular	Botulism Diphtheria Paralytic shellfish Strychnine Tetrodotoxin Thallium
	Mechanical—obstruction	Diphtheria Foreign body (drug packets) Large pill size or large number of pills
	Mechanical—irritation and injury	Caustics Iodine Mercuric chloride Paraquat, diquat

25–3), and the small and large intestines (Table 25–4) is offered in brief in these tables.

THE PANCREAS AND PANCREATIC DISEASE

The pancreas lies in the retroperitoneum, in a transverse fashion, between the second portion of the duodenum and the spleen. The gland serves both exocrine and endocrine functions, with the secretion of pancreatic juice and enzymes as exocrine functions, and the secretion of insulin, glucagon, and other hormones as endocrine functions. The pancreatic acini contain cells that produce digestive enzymes, which flow to the duodenum through the pancreatic ducts. Endocrine cells are found in the islets of Langerhans, which are found diffusely throughout the pancreas.

The presence of partially digested food in the duodenum leads to the release of cholecystokinin and subsequent stimulation of pancreatic secretion and fluid flow, among other effects. Pancreatic enzyme activities are further regulated by the secretion of inactive precursors, which require activation in the intestinal lumen. This is accomplished by the action of trypsin, after the activation of trypsinogen by enterokinase in the duodenum. Amylase and lipase are the only pancreatic enzymes to be secreted in active form.

Pancreatitis connotes tissue damage and inflammation. Interstitial pancreatitis features edema and inflammation histologically, plus acinar cell necrosis. In contrast, hemorrhagic pancreatitis features more widespread necrosis and widespread tissue hemorrhage and vascular thrombosis.

TABLE 25–3. Xenobiotics That Affect the Stomach

Type of Effect	Mechanism	Examples
Pain	Epigastric pain fiber stimulation	Alcohols Antineoplastics Arsenic Caustics Colchicine Iron Mercuric chloride NSAIDs Podophyllin Salicylates
	Perforation (peritonitis)	Caustics Salicylates
	Obstruction	Bezoars Foreign body NSAIDs Salicylates
Vomiting	Local stimulation	Caustics Colchicine Detergents/soap (strong) Fluoride Metals (iron, mercury, thallium, arsenic) Mushrooms Salicylates Solvents Staphylococcal exotoxin Zinc chloride
	Central chemoreceptor trigger zone	Cardioactive steroids CO (?) Opioids Nicotine
	Local and central	Methylxanthines Syrup of ipecac
	Increased intracranial pressure	
	Toxin-induced hemorrhage	Amphetamine Cocaine Ephedrine
	Edema	Vitamin A Postanoxic brain injury
	Hemorrhage or infarct Hypertension Hypotension Coagulopathy	Anticoagulants Crotaline envenomation
Hematemesis	Direct mucosal injury	Alcohols (ethanol, isopropyl) Caustics Metals Plants Radiation Salicylates and NSAIDs Zinc chloride
	Coagulopathy	Anticoagulants Hepatic failure

TABLE 25–4. Xenobiotics That Affect the Small and Large Intestines

Type of Effect	Mechanism	Examples
Pain	Increased contraction	
	Local irritation	Caustics Colchicine Metals Mushrooms Solanine-containing plants Stimulant cathartics
	Cholinergic stimulation	Cholinergics Opioid withdrawal
	Obstruction	Foreign body/drug-containing packets
Diarrhea	Mechanical irritation and injury	Bacterial endo- and exotoxins (food poisoning) Cathartic stimulants Caustics Colchicine Metals Mushrooms Solanine-containing plants
	Failure of mucosal regeneration	Colchicine Daunorubicin Etoposide Fluorouracil Ionizing radiation Podophyllin
	Cholinergic stimulation	Cholinergics Nicotine Opioid withdrawal
	Other mechanisms	Methylxanthines
Constipation	Local effects	Fluid and electrolyte depletion Opioids
	Central effects	Anticholinergics Infant botulism CNS depressants

Although there are multiple etiologies underlying acute pancreatitis, alcohol and gallstones are the most important. The specific effects of alcohol are uncertain, but may include hypersecretion, sphincter of Oddi spasm, hypertriglyceridemia, and others. The delivery of ethanol to the pancreatic interstitium and ductal space results in premature release of free fatty acids, hypertriglyceridemia, and subsequent epithelial damage.

Drug-induced pancreatitis is a broad topic with multiple xenobiotics, whose association with disease can be listed as definite, likely, or possible (Table 25–5). The pathogenic mechanism varies with the specific drug, although some drugs, such as the nucleoside reverse transcriptase 2,3-dideoxyinosine, may promote pancreatitis as a result of mitochondrial toxicity. Overstimulation is recognized with exposure to cholinesterase inhibitors, such as parathion or scorpion venom, while vasospasm, secondary to ergot alkaloids, is also reported.

TABLE 25–5. Xenobiotics Associated with Pancreatitis

Exocrine Pancreas	Endocrine (Islets of Langerhans) Pancreas
Alcohols	**Alpha cells**
Ethanol	Cobalt salts
Methanol	Decamethylene diguanidine
	Phenylethylbiguanide
Analgesics and NSAIDs	
Acetaminophen	**Beta cells**
Opioids	Alloxan
Salicylates[a]	Androgens
Sulindac	Cyclizine
	Cyproheptadine
Antibiotics	Diazoxide
Pentamidine	Dihydromorphanthridine
Rifampin	Epinephrine
Sulfonamides	Glucagon
Tetracycline	Glucocorticoids
	Growth hormone
Anticonvulsants	Pentamidine
Valproic acid	Streptozocin
	Sulfonamides
Antihypertensives	Vacor
ACE inhibitors	Zinc chelators
Diazoxide[a]	
Methyldopa[a]	**Delta cells**
	None known
Antimitotics	
Azathioprine	
L-Asparaginase	
Mercaptopurine	
Antivirals for HIV disease	
Nucleoside reverse transcriptase inhibitors	
Didanosine	
Zalcitabine	
Zidovudine	
Diuretics	
Chlorthalidone[a]	
Ethacrynic acid[a]	
Furosemide	
Thiazides	
Hormones	
Corticosteroids	
Estrogens	
Others	
Organic phosphorous compounds	
Phenformin	

[a]Based on single or rare case reports.

Modified after Riddell RH, Strauss FH: The pancreas. In: Riddell RH, ed: Pathology of Drug-Induced and Toxic Diseases. New York. Churchill Livingstone, 1982, pp. 611–629.

DIRECT TOXICITY TO THE GI TRACT

There are several important categories of xenobiotics that are directly toxic to the GI tract, including "traditional agents," such as caustics, ethanol, and other alcohols. In recent years, the potential damage of biologic, chemical, or radiologic weapons to the body in general, and to the GI tract in particular, has become a great concern.

FOREIGN BODIES

For obvious reasons, the esophagus is the site of most foreign bodies, which may become lodged in the cervical esophagus, at the level of the aortic notch, just above the gastroesophageal junction, or just proximal to an esophageal narrowing. The major symptoms related to foreign objects in the upper GI tract are pain, bleeding, perforation, and obstruction. The general rule is that nonoperative means can be employed for up to 12 hours, after which time surgery should be considered, as the chances of tissue necrosis and perforation increase after this time.

Foreign bodies also are commonly found in the stomach. Many small foreign bodies will pass through the stomach and the rest of the GI tract without problems, although objects larger than 5 cm in the largest diameter or 2 cm in the smallest diameter may not be able to traverse the duodenum and must be removed endoscopically or surgically.

Once in the small intestine, the narrowest area and a site for obstruction is the ileocecal valve, whose maximal opening is about 2.5 cm. Probably the most common type of "foreign" body to become impacted at the ileocecal valve is a large gallstone, which gives rise to "gallstone ileus."

ANTIEMETICS

Although antiemetic therapies are not usually considered in discussions of toxicology, they may play a role in the management of symptoms related to xenobiotics. A number of antiemetics, with differing mechanisms of activity, have been developed. Phenothiazines and butyrophenones prevent nausea and vomiting via CNS dopamine antagonism. Metoclopramide (Reglan) is a substituted benzamide and procainamide derivative with a variety of central and peripheral effects, predominantly dopamine antagonism, but also 5-hydroxytryptamine type 3 (5-HT_3)-receptor antagonism and cholinomimetic effects. Anticholinergics, such as transdermally administered scopolamine, are not antiemetics but decrease the sensation of nausea, especially related to motion sickness. Based on studies that show that nausea and vomiting may be mediated via 5-HT_3 receptors, located particularly in the area postrema, a number of 5-HT_3 antagonists, such as ondansetron, have been developed and are in wide clinical use.

26 Hepatic Principles

The liver has an essential role in the maintenance of physiologic homeostasis. Its functions include the synthesis, storage, and breakdown of glycogen; the metabolism of lipids; the synthesis of albumin, clotting factors, and other important proteins; synthesis of the bile acids necessary for the absorption of lipids and fat-soluble vitamins; the metabolism of cholesterol; the excretion of metals, most importantly iron, copper, zinc, manganese, mercury, and aluminum; and the detoxification of products of metabolism, such as bilirubin and ammonia. Generalized disruption of these important functions results in familiar manifestations of liver failure: hyperbilirubinemia, coagulopathy, hypoalbuminemia, hyperammonemia, and hypoglycemia. Disturbances of more specific functions result in accumulation of fat, toxic metals, hypercholesterolemia, and fat-soluble vitamin deficiencies.

The liver is also the primary site of biotransformation and detoxification of xenobiotics. It contains the highest concentration of enzymes involved in phase I oxidation–reduction reactions. Its interposition between the gut and systemic circulation makes it the first-pass recipient of xenobiotics absorbed from the gastrointestinal tract into the portal vein. The liver also receives blood from the systemic circulation and participates in the detoxification and elimination of xenobiotics that reach the bloodstream through other routes, such as inhalation or cutaneous absorption. Many detoxified xenobiotics are excreted in the urine. In addition, the biliary tract provides a second essential route for the elimination of detoxified xenobiotics and products of metabolism.

Many xenobiotics are lipophilic, inert substances requiring chemical activation to make them sufficiently soluble to be eliminated. This is accomplished by conjugation of the reactive product of phase I biotransformation with a molecule such as glucuronide that facilitates renal or biliary excretion. Although phase I activation followed by phase II conjugation usually results in detoxification of these xenobiotics, it occasionally leads to the production of xenobiotics with increased toxicity, which is often manifest at the site of their synthesis. Because of its location at the end of the portal system and its substantial complement of biotransformation enzymes, the liver is especially vulnerable to toxic injury.

MORPHOLOGY AND FUNCTION OF THE LIVER

Approximately 75% of the blood supply to the liver is derived from the portal vein, which drains the alimentary tract, spleen, and pancreas. This blood is enriched with nutrients and other absorbed xenobiotics and is poor in oxygen. Oxygen content diminishes several-fold as blood flows from the portal area to the central vein, affecting the localization of oxygen-dependent mechanisms of injury. When immunologically activated by xenobiotics, Kupffer cells (macrophages) contribute to the generation of oxygen free radicals and may also participate in the production of autoimmune injury to hepatocytes. Ito cells found between the endothelial cells and hepatocytes are a primary site for the storage of fat and vitamin A.

Two basic pathologic concepts are used to describe the appearance and function of the liver: a structural one represented by the hepatic lobule, and a functional one represented by the acinus. The basic morphologic unit of the liver

characterized by light microscopy is the hepatic lobule, a hexagon with the hepatic vein at the center and the portal triads at the angles. Cords of hepatocytes are oriented radially around the hepatic vein. The acinus, or "metabolic lobule," is a functional unit of the liver. Located between two central veins, it is bisected by terminal branches of the hepatic artery and portal vein that extend from the bases of the acini toward hepatic venules at the apices. The acinus is subdivided into three metabolically distinct zones. Zone 1 lies near the portal triad, zone 3 near the central vein, and zone 2 is intermediate. Figure 26–1 provides a visual illustration of the relationship of these structural and functional concepts of the liver. The different metabolic functions of these zones and the cellular location of biotransformation reactions affect the anatomic distribution of liver injury produced by xenobiotics. There is useful correlation between these anatomic and functional conceptualizations of the liver. Hepatocellular injury that occurs near the portal vein is called *periportal necrosis*. This term describes injury in zone 1. The terms *centrilobular* and *zone 3* necrosis refer to injury that surrounds the central vein (Table 26–1).

FACTORS THAT AFFECT THE DEVELOPMENT OF HEPATOTOXICITY

Xenobiotics such as acetaminophen, carbon tetrachloride (CCl_4), and yellow phosphorus that produce liver damage in all humans in a predictable and dose-dependent manner are called *intrinsic hepatotoxins*. Those that cause liver damage in a small number of individuals and whose effect is not apparently dose dependent or predictable are called *idiosyncratic hepatotoxins*. Sporadic unpredicted hepatotoxicity is not really "idiosyncratic," but more likely a result of the combined effects of genetic and other factors that result in the overproduction or decreased clearance of toxic metabolites. Idiosyncratic toxicity is related to individual variability in the capacity to metabolize a specific xenobiotic and would be predictable, rather than "idiosyncratic," if the exposed individual's metabolic capabilities could be prospectively defined.

Hypersensitivity

Immune-mediated liver injury is an idiosyncratic and host-dependent hypersensitivity response to exposure to xenobiotic. It is differentiated from liver injury caused by other autoimmune disorders by the absence of self-perpetuation; that is, the need for continuous exposure to the xenobiotic to perpetuate the injury. Hypersensitivity reactions result in forms of liver injury that include hepatitis, cholestasis, and mixed disorders. Drugs with hypersensitivity reactions that typically present with hepatitis include halothane, trimethoprim-sulfamethoxazole, anticonvulsants, and allopurinol. Drugs that typically present with cholestatic signs and symptoms (pruritus, jaundice, insignificant elevations of aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) include chlorpromazine, erythromycin, penicillins, rifampin, and sulfonamides. Signs of injury typically begin 1–8 weeks following the initiation of the drug, although they may begin as late as 20 weeks for drugs such as isoniazid (INH) or dantrolene.

Availability of Substrates

The availability of substrates for detoxification may significantly affect the likelihood of hepatic injury. In healthy adults taking therapeutic amounts of acetaminophen, approximately 90% of hepatic metabolism results in formation of

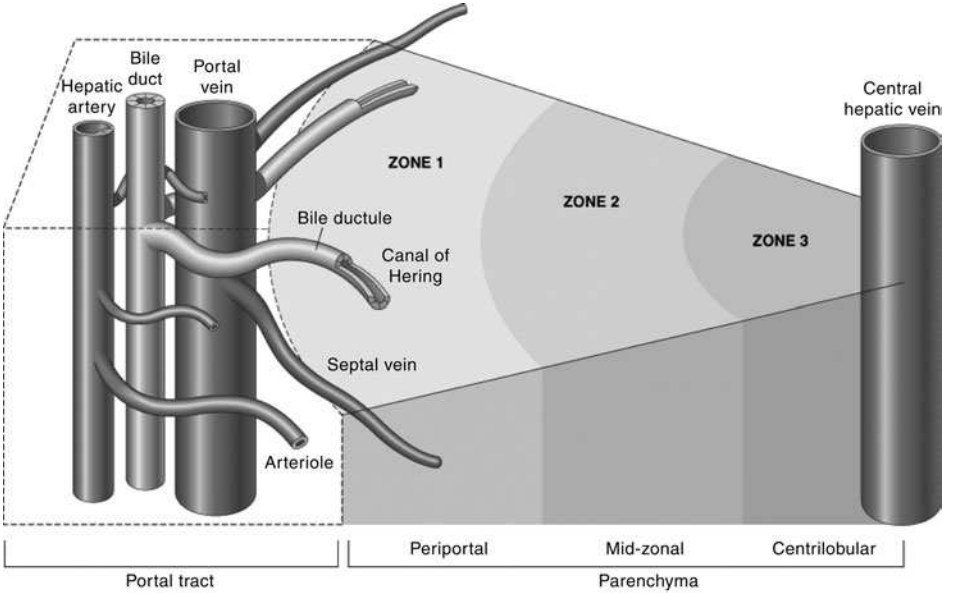

FIG. 26–1. The acinus is defined by three functional zones. Specific contributions of each zone to the biotransformation of xenobiotics reflect the declining oxygen content of blood as it flows along sinusoids from the oxygen-rich portal area to the central hepatic vein. Hepatocytes that form the parenchyma of these three zones also have enzymatic and metabolic functions that are specific to each of the three zones. The hepatic lobule (not shown) is a structural concept, a hexagon with the central vein at the center surrounded by 6 portal areas that contain branches of the hepatic artery, bile duct, and portal vein. Injury to hepatocytes that is confined to zone 3 is called "centrilobular," because in the structure of the lobule, zone 3 encircles the central vein, which is the center of the hepatic lobule. *(Adapted with permission from Crawford JM: The liver and the biliary tract. In: Kumar V, Fausto N, Abbas A, eds: Robbins and Cotran's Pathologic Basis of Disease, 7th ed. Philadelphia, Elsevier, 2004, Fig. 18.1, p. 879.)*

TABLE 26–1. Metabolic Zones of the Liver

Zone	Location	Biochemistry	Types of Injury
1	Periportal	High oxygen content High glutathione content	Oxygen free radical–mediated necrosis
2	Mid-zonal	Shared functions, zones 1 and 3	Shared functions, zones 1 and 3
3	Centrilobular	Low oxygen content High capacity of glucuronidation and sulfation	Necrosis caused by toxic metabolites of CYP2E1
		High CYP2E1, alcohol dehydrogenase	Increased CCl_4 and ethanol injury caused by reducing environment

glucuronidated or sulfated metabolites. Most of the remainder undergoes oxidative metabolism to the toxic electrophile *N*-acetyl-*p*-benzoquinoneimine (NAPQI) and is rapidly detoxified by conjugation with glutathione. Glutathione may be depleted during the course of metabolism of acetaminophen by otherwise normal livers, or it may be decreased by inadequate nutrition or liver disease. Excessive amounts of acetaminophen result in increased synthesis of NAPQI, which in the absence of glutathione reacts avidly with hepatocellular macromolecules. The cellular concentration of glutathione correlates inversely with the demonstrable covalent binding of NAPQI to liver cells.

MORPHOLOGIC AND BIOCHEMICAL MANIFESTATIONS OF HEPATIC INJURY

There are only a limited number of ways that the liver responds to injury. Cells may swell (ballooning degeneration) and accumulate fat (steatosis) or biliary material. They may necrose and lyse, or undergo the slower process of apoptosis, forming shrunken, nonfunctioning, eosinophilic bodies. Necrosis may be focal or bridging, linking the periportal or centrilobular areas, zonal or panacinar, or it may be massive. An inflammatory cell response may precede or follow necrosis. Injury to the bile ducts results in cholestasis. Vascular injuries can cause obstruction to venous or arterial flow. Table 26–2 lists characteristic morphologies of hepatic injury and associated xenobiotics.

Acute Hepatocellular Necrosis

Acute necrosis of a hepatocyte disrupts all aspects of its function. Because there is a great deal of functional reserve in the liver, hepatic function may be preserved despite the development of focal necrosis.

Steatosis

Steatosis is the abnormal accumulation of fat in hepatocytes. It occurs in a number of metabolic conditions that include responses to xenobiotics. Two forms of steatosis are described; macrovesicular steatosis, in which the nucleus is displaced by accumulation of intracellular fat, and microvesicular steatosis, which is characterized by fat droplets that do not displace the nucleus. The intracellular fat accumulation reflects abnormal hepatocellular metabolism and may occur as a result of any one or more of the following mechanisms: impaired synthesis of lipoproteins; increased mobilization of peripheral adipose stores; increased uptake of circulating lipids; increased triglyceride production; decreased binding of triglycerides to lipoprotein; decreased release of very-low-density lipoproteins

TABLE 26–2. Morphology of Liver Injury Caused by Common Xenobiotics

Acute Hepatocellular Necrosis	**Microvesicular Steatosis**	**Fibrosis**
Acetaminophen	Aflatoxin	Ethanol
Allopurinol	Fialuridine	Methotrexate
Carbamazepine	Hypoglycin	Vitamin A
Carbon tetrachloride	Nucleoside analogs (antiretrovirals)	**Neoplasms**
Cyclopeptide-containing mushrooms	Valproic acid	Androgens
Halothane		Contraceptive steroids
Hydralazine	**Granulomatous Hepatitis**	Vinyl chloride
Infliximab	Allopurinol	**Venoocclusive Disease**
Iron	Diltiazem	Pyrrolizidine alkaloids
Isoniazid	Hydralazine	Cyclophosphamide
Methotrexate	Isoniazid	
Phosphorus (yellow)	Methyldopa	**Cholestasis**
Sulfonamides	Nitrofurantoin	Amoxicillin/clavulanic acid
Troglitazone	Quinidine	Androgens
Steatohepatitis	Quinine	Chlorpromazine
Amiodarone	Sulfonamides	Chlorpropamide
Ethanol		Erythromycin estolate
Vitamin A		Hydralazine
		Nitrofurantoin
		Oral contraceptives

from the hepatocytes, and decreased β-oxidation of fatty acids. Steatosis is a condition that is usually well tolerated by hepatocytes and is reversible following withdrawal of the precipitant. Common xenobiotics associated with macrovesicular steatosis include ethanol and amiodarone.

Cholestasis

Cholestatic injury is manifested primarily by jaundice and pruritus and is a manifestation of general failure of liver function. More specific mechanisms that are postulated to result in cholestasis include (a) impairment of the integrity of tight membrane junctions that functionally isolate the canaliculus from the hepatocyte and sinusoids; (b) failure of transport of bile components across the hepatocytes; (c) blockade of specific membrane active transport sites; (d) decreased membrane fluidity resulting in altered transport; and (e) decreased canalicular contractility resulting in decreased bile flow.

Venoocclusive Disease

Hepatic venoocclusive disease is caused by toxic injury to the endothelium of terminal hepatic venules that results in intimal thickening, edema, and nonthrombotic obstruction. Hepatic venoocclusive disease is rapidly fatal in 15–20% of cases.

Peliosis Hepatis

Peliosis hepatis is characterized by large, blood-filled cavities associated with sinusoidal dilation (Chap. 44). It is most frequently associated with the use of

androgenic steroids. Although most patients are asymptomatic, occasionally the dilated sinusoids rupture and cause hemoperitoneum.

Cirrhosis

Cirrhosis, which results in irreversible hepatic dysfunction and portal hypertension, is caused by progressive fibrosis and scarring of the liver. Fibrosis is related to increased production of collagen.

CLINICAL PRESENTATIONS

Two general types of clinical patterns occur with hepatic toxins; a chronic indolent progression of injury that may elude diagnosis, and a more acute, sometimes fulminant, progression of injury that is temporally related to exposure to the xenobiotic.

Chronic injury is associated with an initially asymptomatic or minimally symptomatic clinical state, with mildly abnormal liver chemistries and slow progression to clinically evident liver dysfunction or cirrhosis. Over a period of time ranging from months to years, jaundice, coagulopathy, encephalopathy, hepatomegaly, or signs of cirrhosis, such as spider angiomata, ascites, caput medusa, and gynecomastia, may be evident. An indolent progression to cirrhosis with minimal symptoms occurs in some patients with chronic exposures to vitamin A, methotrexate, ethanol, amiodarone, and methyldopa.

Symptoms of acute liver injury include fever, anorexia, nausea, vomiting, and fatigue. Signs include coagulopathy, jaundice, percussion tenderness in the right upper quadrant, and encephalopathy. Rapid development of portal hypertension, ascites, and death follows the onset of some cases of venoocclusive disease. Patients with acute, large exposures to carbon tetrachloride, yellow phosphorus, acetaminophen, and cyclopeptide-containing mushrooms initially manifest gastrointestinal symptoms. This is followed by a period of well-being (1–3 days). Then signs of acute hepatic and renal failure with fatigue, anorexia, and nausea are followed by profound jaundice, hemorrhage, ascites, hepatic encephalopathy, and death. Patients with significant acute occupational exposure to dimethylformamide present with abdominal pain, anorexia, and disulfiram-type reactions.

Fulminant hepatic failure (FHF) is defined as liver injury that progresses to encephalopathy within 8 weeks of the onset of illness in a patient without preexisting liver disease. Complications from fulminant hepatic failure include encephalopathy, cerebral edema, coagulopathy, renal dysfunction, hypoglycemia, hypotension, acute lung injury, sepsis, and death. In some cases, a patient may progress from health to death in as little as 2–10 days.

THE EVALUATION OF THE PATIENT WITH LIVER DISEASE

The history is critical in establishing the diagnosis of the patient with liver disease. A medication and herbal history, especially a history of acetaminophen, should be obtained. An occupational history might indicate a hepatotoxic exposure (Table 26–3). Alcohol abuse is a common cause of acute hepatitis and the most common cause of cirrhosis in this country.

Clinical Laboratory

Laboratory tests are helpful and certain patterns may be suggestive of specific etiologies (Table 26–4).

TABLE 26–3. Occupational Exposures Associated with Liver Injury

Xenobiotic	Type of Injury
Arsenic	Cirrhosis, angiosarcoma
Beryllium	Granulomatous hepatitis
Carbon tetrachloride	Acute necrosis
Chlordecone	Minor hepatocellular injury
Copper salts	Granulomatous hepatitis, angiosarcoma
Dimethylformamide	Steatohepatitis
Methylenedianiline	Acute cholestasis
Phosphorus	Acute necrosis
Tetrachloroethane	Acute, subacute necrosis
Tetrachloroethylene	Acute necrosis
Toluene	Steatosis, minor hepatocellular injury
Trichloroethane	Steatosis, minor hepatocellular injury
Trinitrotoluene	Acute necrosis
Vinyl chloride	Acute necrosis, fibrosis, angiosarcoma
Xylene	Steatosis, minor hepatocellular injury

Aminotransferases

Elevation of hepatocellular enzymes, especially AST and ALT, indicates hepatocellular injury, and within a given clinical context, has useful diagnostic significance. Aminotransferases may be increased up to 500 times normal when hepatic necrosis is extensive, such as in severe acute viral or toxic hepatitis. The degree of elevation does not always reflect the severity of injury as concentrations may decline as fulminant hepatic failure progresses. Processes associated with intrahepatic cholestasis in the absence of hepatitis also may not lead to significant aminotransferase elevation. In contrast to other forms of hepatitis, in alcoholic liver disease, the AST level is typically 2–3 times greater than the ALT concentration.

Alkaline Phosphatase

In patients with cholestasis, bile acids stimulate the synthesis of alkaline phosphatase by hepatocytes and biliary epithelium in response to a number of pathologic processes in the liver. Elevations of the alkaline phosphatase as high as 10-fold may occur with infiltrative liver diseases, but are most commonly associated with extrahepatic obstruction.

Bilirubin

Elevation of conjugated, or direct, bilirubin implies impairment of secretion into bile, whereas elevation of unconjugated, or indirect, bilirubin implies impairment of conjugation. Except in cases of pure unconjugated hyperbilirubinemia, the fractionation of bilirubin, in the case of hepatobiliary disorders, does not have any important diagnostic utility, and will not distinguish patients with parenchymal disorders of the liver from intrinsic or extrinsic cholestasis. The presence of bilirubin in the urine implies elevation of conjugated or direct bilirubin and obviates the need for laboratory fractionation.

Serum Albumin

Quantitatively, albumin is the most important protein that is made in the liver. With a half-life of up to 20 days, the albumin is usually normal in the previously healthy patient with acute liver injury. In the absence of other disorders that affect albumin, such as nephrotic syndrome, protein-losing enteropathy, or starvation, a low serum albumin is a useful marker for the severity of chronic liver disease.

TABLE 26–4. Laboratory Tests That Can Be Used to Evaluate the Liver

Disorder	Alkaline Phosphatase	AST, ALT	Albumin	Prothrombin Time	Bilirubin	Ammonia	Anion Gap
Hepatocellular necrosis, acute focal (hepatitis)	N or ↑	↑↑↑	N	N or ↑	↑↑	N	N
Hepatocellular necrosis, acute massive	N or ↑	↑↑↑	N	↑↑	↑↑↑	↑↑	↑
Chronic infiltrative disease (tumor, fatty liver)	↑↑	↑	N	N	N	N	N
Microvesicular steatosis, acute	N or ↑	↑↑	↓	↑↑	↑	↑↑	↑↑↑
Cholelithiasis	↑↑	↑	N	N	N or ↑	N	N
Cholestatic hepatitis	↑↑	↑	N	N	↑	N	N
Chronic hepatitis	N or ↑	↑	N or ↓	N	N or ↑	N	N
Cirrhosis	N or ↑	↑	↓	N or ↑	N or ↑	N or ↑	N

↑ = increase; ↓ = decrease; N = normal.

TABLE 26–5. Stages of Hepatic Encephalopathy

Clinical Stage	Mental Status	Neuromotor Function
Subclinical	Normal physical examination	Subtle impairment of neuromotor function → driving or work injury hazard
I	Euphoric, irritable, depressed, fluctuating mild confusion, poor attention, sleep disturbance	Poor coordination; may have asterixis alone
II	Impaired memory, cognition, simple mathematical tasks	Slurred speech, tremor, ataxia
III	Difficult to arouse, persistent confusion, incoherent	Hyperactive reflexes, clonus, nystagmus
IV	Coma; may respond to noxious stimuli	May have decerebrate posturing; Cheyne-Stokes respirations; pupils are typically reactive and the oculocephalic reflex is intact; may have signs of ↑ intracranial pressure

Coagulation Factors

Impairment of coagulation is a marker of the severity of hepatic dysfunction in both acute and chronic liver disease. Unlike the serum albumin with its half-life of 20 days, the onset of coagulopathy as a consequence of impaired synthesis of the short-lived vitamin K–dependent clotting factors II, VII, IX, and X is rapid. Very acute changes in coagulation reflect the concentration of factor VII, which has the shortest half-life.

Ammonia

Severe generalized impairment of hepatic function leads to a rise in the serum ammonia concentration, as a result of impairment of detoxification of ammonia produced during catabolism of proteins. The absolute level of elevation is not clearly associated with mental status alteration. Elevations of serum ammonia concentrations occur in only 60–80% of patients with hepatic encephalopathy, suggesting that ammonia may be a marker rather than a primary cause of CNS dysfunction.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) is a severe but potentially fully reversible manifestation of liver failure, even in cases of deep coma. Table 26–5 describes the clinical stages of acute HE in detail.

MANAGEMENT

In many cases, toxic liver injury resolves with simple withdrawal of the offending xenobiotic. In cases of severe injury, significant improvement in survival is associated with good supportive care in an intensive care environment. Early referral to a transplant center for patients with evidence of severe or rapidly progressive toxic injury is indicated.

27 Renal Principles

OVERVIEW OF RENAL FUNCTION

The kidneys maintain the constancy of the extracellular fluid by creating an ultrafiltrate of the plasma that is virtually free of cells and larger macromolecules, and then processing that filtrate, reclaiming what the body needs and letting the rest escape as urine. Every 24 hours, an adult's kidneys filter about 180 L of water (total body water is about 25–60 L) and 25,000 mEq of sodium (total body Na^+ is 1200–2800 mEq). Under normal circumstances the kidneys regulate these two substances independently of each other, depending on the body's needs.

Renal function begins with filtration at the glomerulus, a highly permeable capillary network stretched between two arterioles in series. The relative constriction or dilation of these vessels normally controls the glomerular filtration rate (GFR). The filtrate then enters a series of tubules that reabsorb most of it and secrete certain substances, such as organic acids and bases, into the urinary space. The proximal tubule performs bulk reabsorption, reclaiming isotonically 65–70% of the filtrate; distal to that are the loop of Henle, which controls concentration and dilution of the urine, and the distal nephron, which does the fine-tuning in the balance between excretion and reclamation. Reabsorption of sodium is controlled proximally by hydrostatic and oncotic pressures in the peritubular capillaries, and distally by hormones such as aldosterone. Control of water reclamation depends first on function of the ascending limb of the loop of Henle, which absorbs solute without water. This produces a dilute tubular fluid and at the same time makes the medullary interstitium hypertonic. Final regulation of water reabsorption is related to the level of antidiuretic hormone (ADH), which inserts water-reabsorbing channels (aquaporins) into the membranes of the final nephron segments (collecting ducts). The kidneys also regulate balance for potassium, hydrogen ion, calcium, and phosphate balance.

Injury to either the glomeruli or the tubules may lead to renal dysfunction; that is, to a decrease in glomerular filtration. As the kidneys fail, serum concentrations of the marker substances urea and creatinine increase. However, the relationship between these concentrations and the actual GFR is hyperbolic, not linear, so a small, initial elevation in serum concentrations of these substances denotes a large decrease in renal function. By the time blood urea nitrogen (BUN) or serum creatinine exceeds the upper limit of normal, GFR is already reduced by more than 50%.

Many xenobiotics cause or aggravate renal dysfunction. The kidneys are particularly susceptible to toxic injury for 4 reasons: (a) they receive 20–25% of cardiac output yet make up less than 1% of total body mass; (b) they are metabolically active, and thus vulnerable to agents that disrupt metabolism; (c) they remove water from the filtrate and may build up a high concentration of xenobiotics; and (d) the glomeruli and interstitium are susceptible to attack by the immune system.

Functional Toxic Renal Disorders

Although most toxic renal injury results in decreased renal function, there are 3 functional disorders that upset body balance despite normal GFR in ana-

tomically normal kidneys: renal tubular acidosis; syndrome of inappropriate secretion of antidiuretic hormone; and nephrogenic diabetes insipidus.

Renal tubular acidosis (RTA) is a loss of ability to reclaim the filtered bicarbonate (proximal RTA) or a decreased ability to generate new bicarbonate to replace that lost in buffering the daily acid load (distal RTA). In either case, there is a nonanion-gap metabolic acidosis, usually accompanied by hypokalemia.

Syndrome of inappropriate antidiuretic hormone (SIADH) occurs when the body produces ADH despite a fall in plasma osmolality, which normally inhibits ADH secretion. ADH primarily affects the collecting tubule and causes increased water reabsorption by increasing the aquaporin channels in this segment. The main clinical manifestations of SIADH are a concentrated urine (as reflected in a relative increase in urine osmolality) and hyponatremia in the face of euvolemia (Chap. 17).

Nephrogenic diabetes insipidus (NDI) is the reverse of SIADH. It denotes inability of the kidneys to respond to ADH stimulation despite severe losses of body water. There are may causes of nephrogenic diabetes insipidus, including xenobiotics (Chap. 17).

MAJOR TOXIC SYNDROMES OF THE KIDNEY

Most nephrotoxicity involves histologic renal injury. Although xenobiotics may affect any part of the nephron (Fig. 27–1), there are three major syndromes of toxic renal injury: (a) chronic renal failure; (b) nephrotic syndrome; and, especially, (c) acute renal failure (Table 27–1). Nephrotoxins usually affect the most metabolically active segment of the nephron—the tubules; consequently, most nephrotoxicity involves either acute or chronic tubular injury, although glomerular injury may also sometimes result from xenobiotics.

Chronic renal failure refers to any disease process that causes progressive decline of renal function over a period of months to years. There is usually a gradual rise in BUN and serum creatinine as glomerular filtration falls; often there are no symptoms other than nocturia (indicating loss of urinary concentrating ability). The most common lesion of nephrotoxic chronic renal failure is chronic interstitial nephritis.

Nephrotic syndrome is characterized by massive proteinuria (>3 g/d in the adult), hypoalbuminemia, hyperlipidemia, and the edema that usually prompts the patient to seek medical attention. Although the relationships among these findings are incompletely understood, the underlying event is injury to the glomerular barrier that normally prevents macromolecules from passing from the capillary lumen into the urinary space. The tubules also retain sodium, causing expansion of the extracellular space and edema. Table 27–2 lists xenobiotics that induce nephrotic syndrome.

Acute renal failure is defined as any abrupt decline in renal function that impairs the capacity of the kidney to maintain metabolic balance. The 3 main categories of acute renal failure are prerenal, postrenal, and intrinsic renal failure. *Prerenal failure* involves impaired renal perfusion, such as in volume depletion, shock, or congestive heart failure. *Postrenal failure,* such as urinary tract obstruction, may result from crystalluria (eg, oxalosis in ethylene glycol poisoning) or blocked urinary flow (eg, bladder dysfunction from anticholinergics). The most common nephrotoxic lesions, however, are *intrinsic renal injuries*, particularly acute tubular necrosis and acute interstitial nephritis (Table 27–1). *Acute tubular necrosis* (Table 27–3), the most common nephrotoxic event, is associated with three different processes: direct toxic

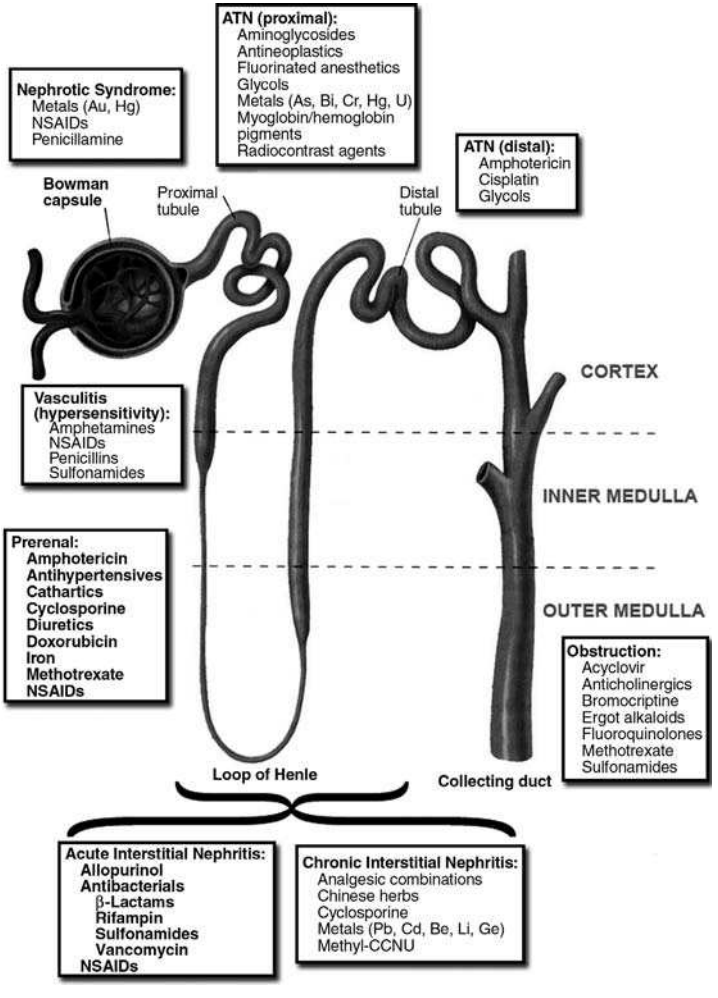

FIG. 27–1. Schematic showing the major nephrotoxic processes and the sites on the nephron that they chiefly affect. ATN = acute tubular necrosis. *(Courtesy of the National Institutes of Health. Drawn by Joseph Lewey.)*

injury, ischemic injury from renal hypoperfusion, and pigmenturia. Direct toxicity accounts for approximately 35% of all cases of acute tubular necrosis. Pigmenturia refers to either myoglobinuria from rhabdomyolysis (skeletal muscle necrosis) or hemoglobinuria from massive hemolysis. Although there is controversy as to how a tubular lesion leads to glomerular shutdown, it is generally felt that tubular obstruction, back-leak of filtrate across injured epithelium, renal hypoperfusion, and decreased glomerular filtering surface combine to impair glomerular filtration.

TABLE 27–1. Major Nephrotoxic Syndromes

Chronic renal failure (slowly increasing azotemia)
Chronic interstitial nephritis
Papillary necrosis
Chronic glomerulosclerosis
Nephrotic syndrome (proteinuria, hypoalbuminemia, edema)
Minimal glomerular change
Membranous nephropathy
Focal segmental glomerulosclerosis
Acute renal failure (rapidly increasing azotemia)
Acute prerenal failure
Acute urinary obstruction
Acute tubular necrosis
Acute interstitial nephritis
Acute vasculitis

TABLE 27–2. Xenobiotics That Cause Nephrotic Syndrome

Captopril
Drugs of abuse (heroin, cocaine)
Metals (gold, mercury)
NSAIDs
Penicillamine

TABLE 27–3. Xenobiotics That Cause Acute Tubular Necrosis

Acetaminophen
Antibacterials
Aminoglycosides
Amphotericin
Pentamidine
Polymyxins
Antineoplastics
Cisplatin
Ifosphamide
Methotrexate
Mithramycin
Streptozotocin
Fluorinated anesthetics
Glycols
Ethylene glycol
Diethylene glycol
Halogenated hydrocarbons
Metals
Arsenic
Bismuth
Chromium
Mercury
Mushrooms
Cortinarius spp
Amanita smithiana
Pigments
Myoglobin
Hemoglobin
Radiocontrast agents
Xenobiotics that cause hypotension or hypovolemia

TABLE 27–4. Xenobiotics That Cause Acute Interstitial Nephritis

More Common	Less Common
Allopurinol	Anticonvulsants
Antibacterials	Carbamazepine
β-Lactams, especially ampicillin, methicillin, penicillin	Phenobarbital
Rifampin	Phenytoin
Sulfonamides	Captopril
Vancomycin	Diuretics
Azathioprine	Ethacrynic acid
NSAIDs	Furosemide
	Thiazides

Clinically, acute tubular necrosis presents as a rapid deterioration of renal function, usually first noted as azotemia. Muddy brown casts or renal tubular cells may be seen in the urinary sediment, but hematuria and leukocyturia are unusual. Disorders of metabolic balance, such as hyperkalemia and metabolic acidosis, are also common.

Acute interstitial nephritis (Table 27–4) is clinically similar to acute tubular necrosis and often must be diagnosed by renal biopsy. Nearly all acute interstitial nephritis is a result of hypersensitivity. In many cases, the renal failure is accompanied by manifestations of systemic allergy, such as fever, rash, and eosinophilia, and finding eosinophils in the urine is consistent with this disorder.

DIFFERENTIAL DIAGNOSIS OF ACUTE RENAL FAILURE

Patients who present with acutely deteriorating renal function often represent a difficult diagnostic challenge. Prerenal failure (renal hypoperfusion) initiates a sequence of events leading to renal salt and water retention. Consequently, prerenal failure is accompanied by low urinary sodium excretion (Table 27–5). Urinary tract obstruction should always be considered when the kidneys fail rapidly. Although complete obstruction leads to anuria, partial obstruction, which is more common, is usually associated with alternating oliguria and polyuria. Continued production of urine in the presence of obstruction leads to distension of the urinary tract above the blockage. Xenobiotics can cause obstruction (Table 27–6).

PATIENT EVALUATION

History

Flank pain, hematuria, and any abnormal pattern of urine output are important symptoms. The patient's intravascular volume status affects renal perfusion. Thus, a history of heart disease or a disorder that lowers plasma volume such as vomiting or diarrhea is important. All current medications should be evaluated for potential renal effects, both directly toxic xenobiotics and xenobiotics such as diuretics that may enhance the toxicity of other substances. A careful occupational history and assessment of hobbies and lifestyle are crucial, with emphasis on exposure to nephrotoxic xenobiotics.

Physical Examination

The patient's hemodynamic status should be carefully assessed. Postural changes in pulse and blood pressure and either engorgement or decreased fill-

TABLE 27–5. Tests of Renal Function

Acute

To differentiate prerenal failure from acute tubular necrosis:

1. BUN-to-creatinine ratio; usually >20:1 in prerenal failure
2. Urine Na^+ usually <20 mEq/L in prerenal failure; usually >40 mEq/L in acute tubular necrosis
3. Fractional Na^+ excretion (FENa) is the most reliable test:

$$FE_{Na} = \frac{\text{Urine [Na]/Plasma [Na}^+\text{]}}{\text{Urine [Creatinine]/Plasma [Creatinine]}} \times 100$$

FE_{Na} <1% (ie, normal) in prerenal failure, if the patient has not received diuretics or large infusions of sodium, which increase Na^+ excretion despite normal tubular function. In tubular necrosis or interstitial nephritis, renal Na^+ absorption is decreased, and FE_{Na} >1%. This is useful except in pigmenturic or iodinated radiocontrast-associated renal failure, when the test is of no benefit.

Chronic

Creatinine clearance (C_{cr}) = U × V/P (normal range 90–130 mL/min), where U is urine creatinine concentration, V is urine flow in mL/min, and P is plasma creatinine concentration. Urine collection must be complete (not necessarily 24 hours), and U and P must be in the same units.

In steady states, C_{cr} can be approximated by estimating a patient's 24-hour creatinine output (~12 mg/kg of body weight in females; ~15 mg/kg of body weight in males), dividing the estimated 24-hour creatinine by the plasma creatinine concentration, and multiplying the result by 0.07 to convert to mL/min; or from the Cockroft-Gault equation:

$$C_{cr} = \frac{(140 - \text{age}) \times \text{ideal body weight (kg)}}{72 \times \text{serum creatinine}} (\times 0.85 \text{ for women})$$

ing of the neck veins give important information about the intravascular volume. The skin should be examined for lesions. Funduscopy may reveal evidence of chronic hypertension or diabetes.

Laboratory Evaluation

The most important parameter of renal function is glomerular filtration. Because urea and creatinine are largely excreted by this route, serum concentrations of these substances are used as markers of renal function. A BUN/creatinine ratio greater than 20 is suggestive of prerenal failure. Because many nephrotoxic xenobiotics are associated with nonoliguric acute renal failure (urine volume >400 mL/d), progressive azotemia without oliguria should always raise suspicion of a drug-related cause. Certain xenobiotics alter measured concentrations of urea and creatinine in the absence of any change in renal function. The most obvious is exogenous creatine taken to build muscle mass. Cefoxitin, nitromethane, and ketones absorb light at the same frequency as the creatinine-reaction product, thus artifactually increasing the measured concentration. Drugs that block renal creatinine secretion, such as cimetidine and trimethoprim, may also increase serum creatinine. BUN may be raised independently of renal function by tetracycline or corticosteroids, which increase protein catabolism.

Examination of the urine is essential in cases of poisoning. Even if urine is sent to the laboratory, it can also be examined carefully by the physician.

TABLE 27–6. Xenobiotics That Cause Urinary Obstruction

Bladder dysfunction	**Crystal deposition**
Anticholinergics	Ethylene glycol
Antihistamines	Fluorinated anesthetics
Antidepressants (cyclic)	Fluoroquinolones
Atropine	Heme pigments
Scopolamine	Indinavir
Antipsychotics	Methotrexate
Butyrophenones	Phenylbutazone
Phenothiazines	Sulfonamides
Bromocriptine	
CNS depressants	**Retroperitoneal fibrosis**
	Ergotamines (methysergide)
	Chinese herbs (*Stephania*)

TABLE 27–7. Examples of Nephrotoxic Medications

Antihypertensives
- Prerenal failure (excessive dosage)
- Acute interstitial nephritis
  - Methyldopa
  - Captopril
- Nephrotic syndrome
  - Captopril
- Obstruction (retroperitoneal fibrosis)
  - Methyldopa

Anticonvulsants
- Acute interstitial nephritis
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
- Nephrotic syndrome
  - Trimethadione
  - Paramethadione

Anesthetics
- Acute tubular necrosis
  - Methoxyflurane
  - Halothane
  - Enflurane

Antineoplastics
- Acute tubular necrosis
  - Cisplatin
  - Methotrexate
  - Mithramycin
  - Ifosfamide
  - Streptozotocin
- Chronic interstitial nephritis
  - Cisplatin
  - Nitrosoureas

(continued)

TABLE 27–7. Examples of Nephrotoxic Medications *(continued)*

Antineoplastics *(cont)*
Thrombotic microangiopathy
Mitomycin C
Diuretics
Prerenal failure (volume depletion)
Acute interstitial nephritis
Acute renal failure (mannitol)
Hyperkalemia (K^+-sparing diuretics)
Hyponatremia
Immunosuppressants
Acute tubular necrosis and/or chronic interstitial nephritis
Cyclosporine
Tacrolimus
Acute interstitial nephritis
Azathioprine
Renal tubular acidosis
Tacrolimus
Radiocontrast agents
Acute renal failure, especially the high-osmolal and ionic agents
Osmotic nephropathy and renal vasoconstriction

Standard dipsticks will detect albumin and glucose. The dipstick test for blood is useful for confirming the presence of small amounts of blood or myoglobin, but it is not a substitute for careful microscopic examination of the sediment. Clinicians should look not only for red or white cells but also for crystals, tubular elements, casts, and bacteria. If acute interstitial nephritis is a consideration, a fresh urine sample should be stained for eosinophils.

Further evaluation of the patient with acute renal failure should include tests for obstruction, which can be caused by a number of substances (Table 27–6). Renal ultrasonography should be performed to look for hydronephrosis. Postvoiding residual urine volume may be measured as appropriate by catheterization or bedside ultrasound; a volume in excess of 75–100 mL may make one suspect bladder dysfunction or obstruction. Table 27–7 lists nephrotoxic complications of specific medications.

28 Genitourinary Principles

The genitourinary system encompasses two major organ systems: the reproductive and the urinary systems. Successful reproduction requires interaction between two sexually mature individuals. Xenobiotic exposures to either individual can have an adverse impact on fertility, which is the successful production of children, and fecundity, which is an individual's or a couple's capacity to produce children. Xenobiotic-related, primary infertility may be the result of effects on the hypothalamic–pituitary–gonadal axis or of a direct toxic effect on the gonads. Fertility is also affected by exposures that cause abnormal sexual performance. Table 28–1 lists the xenobiotics associated with infertility.

MALE FERTILITY

The male reproductive system is composed of the male gonads and the endocrine organs that provide the hormonal controls. Disruption of normal function at any part of the system affects fertility. Spermatogenesis begins with the maturation and differentiation of the germinal spermatogonia. The process is controlled by the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which stimulates the pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH stimulates the development of Sertoli cells in the testes, which are responsible for the maturation of spermatids to spermatozoa. LH promotes production of testosterone by Leydig cells. Testosterone levels must be maintained to ensure the formation of spermatids. Both FSH and testosterone are required for initiation of spermatogenesis, but testosterone alone is sufficient to maintain the process.

Male Sexual Dysfunction

Sexual dysfunction can be a result of decreased libido (sexual desire), impotence, diminished ejaculation, and erectile dysfunction. Libido can be decreased by xenobiotics that block dopaminergic pathways or testosterone production, or by xenobiotics that produce dysphoria. Xenobiotics that affect spinal reflexes can cause diminished ejaculation and erectile dysfunction. Table 28–2 lists xenobiotics associated with sexual dysfunction.

Physiology of Erection

Normal penile erection is a result of both neural and vascular effects leading to smooth muscle relaxation and increased blood flow into the corpora cavernosa sinusoids of the penis. Psychogenic neural stimulation arising from the cerebral cortex is mediated through the thoracolumbar sympathetic and sacral parasympathetic tracts. In animals, dopamine and nitric oxide play a role in erection. Reflex stimulation can also occur from the sacral spinal cord. The afferent limb of the reflex arc is supplied by the pudendal nerves and the efferent limb by the nervi erigentes (pelvic splanchnic nerves). The internal pudendal arteries supply blood to the penis via four branches. When penile blood flow is above 20–50 mL/min, erection occurs. Maintenance of tumes-

TABLE 28–1. Xenobiotics Associated with Infertility

Men		Women	
Xenobiotic	Effects	Xenobiotic	Effects
Anabolic steroids	↓ LH, oligospermia	Antineoplastics	Gonadal toxicity
Androgens	↓ testosterone production	Cyclophosphamide	Ovarian failure
Antineoplastics	Gonadal toxicity	Busulphan	Amenorrhea
Cyclophosphamide	Oligospermia	Combination chemotherapy (MOPP, MVPP)	Amenorrhea
Chlorambucil	Oligospermia		
Methotrexate	Oligospermia	Diethylstilbestrol	Spontaneous abortions
Combination chemotherapy (COP, CVP, MOPP, MVPP)	Oligospermia	Ethylene oxide	Spontaneous abortions
		Lead	Spontaneous abortions, stillbirths
Carbon disulfide	↓ FSH, ↓ LH, ↓ spermatogenesis	Oral contraceptives	Affect hypothalamic–pituitary axis, end-organ resistance to hormones, amenorrhea
Cimetidine	Oligospermia		
Chlordecone	Asthenospermia, oligospermia	Thyroid hormone	↓ Ovulation
Dibromochloropropane (DBCP)	Azoospermia, oligospermia		
Diethylstilbestrol	Testicular hypoplasia		
Ethanol	↓ Testosterone production, Leydig cell damage, asthenospermia, oligospermia, teratospermia		
Ethylene oxide	Asthenospermia (in monkeys), oligospermia		
Ionizing radiation	↓ Spermatogenesis		
Opioids	↓ LH, ↓ testosterone		
Lead	↓ Spermatogenesis, asthenospermia, teratospermia		
Nitrofurantoin	↓ Spermatogenesis		
Sulfasalazine	↓ Spermatogenesis		
Tobacco	↓ Testosterone		

TABLE 28–2. Xenobiotics Associated with Sexual Dysfunction (Particularly Diminished Libido and Impotence)

α-Adrenergic antagonists	Cyclic antidepressants
β-Adrenergic antagonists[a]	Ethanol
Anabolic steroids	Lead
Anticholinergics[a]	Lithium
Anticonvulsants	Monamine oxidase inhibitors[a]
Antiestrogens	Opioids (high dose)
Benzodiazepines	Oral contraceptives
Calcium channel blockers	Phenothiazines
Diuretics	Selective serotonin reuptake inhibitors
Cimetidine	Spironolactone

[a]Associated with erectile dysfunction.

cence occurs with flow rates of 12 mL/min. Penile erection depends on corpus cavernosal smooth muscle relaxation to allow increased blood flow and involves parasympathetic dominance, either by stimulation of parasympathetic receptors or inhibition of the sympathetic axis.

Medications Used in the Treatment of Erectile Dysfunction

Intracavernosal

The three drugs most commonly used intracavernosally for erectile dysfunction are papaverine, prostaglandin E_1, and phentolamine. Papaverine exerts its effects through nonselective inhibition of phosphodiesterase, leading to increased cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels and subsequent cavernosal vasodilation. Systemic side effects include dizziness, nausea, vomiting, hepatotoxicity, lactic acidosis with oral administration, and cardiac dysrhythmias with intravenous use. Intracavernosal administration is associated with penile fibrosis and the development of priapism. Prostaglandin E_1 (alprostadil) is a nonspecific agonist of prostaglandin receptors resulting in increased concentrations of intracavernosal cAMP, cavernosal smooth muscle relaxation, and penile erection. Penile fibrosis can occur but the incidence is lower compared to papaverine. Other adverse effects include penile pain, secondary to its effects as a nonspecific prostaglandin receptor agonist, and priapism. Phentolamine is a competitive α-adrenergic antagonist at α_1 and α_2 receptors. It effects erection by inhibiting the normal resting adrenergic tone in cavernosal smooth muscle, thus allowing increased arterial blood flow and erection. Intracavernosal use can cause systemic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset. Penile fibrosis and priapism are also reported.

Oral

Phosphodiesterase 5 Inhibitors Since the development of the phosphodiesterase 5 inhibitors, oral therapy has replaced intracavernosal injections as the mainstay for treatment of erectile dysfunction. Phosphodiesterase 5 inhibitors increase nitric oxide–induced cGMP levels by preventing phosphodiesterase breakdown of cGMP, enhancing nitric oxide–induced vasodilation to promote penile vascular relaxation and erection.

The most common adverse effects of the phosphodiesterase 5 inhibitors are headache, flushing, dyspepsia, and rhinitis, which are related to phos-

phodiesterase 5 inhibitory effects on extracavernosal tissue. Vardenafil is associated with infrequent abnormal vision, such as haziness. Blurred or color vision is not reported with tadalafil. Tadalafil use is associated with anterior ischemic optic neuropathy. More serious adverse effects of this class include myocardial infarction, when used alone or with nitrates, hypertrophic subaortic stenosis obstruction, priapism, and optic ischemia.

Yohimbine Yohimbine, an indole alkylamine alkaloid from the West African yohimbe tree (*Corynanthe yohimbe*), is an α_2-adrenergic antagonist with cholinergic activity used to treat erectile dysfunction and postural hypotension associated with anticholinergic drugs.

Adverse effects can occur with relatively low doses of yohimbine. Tachycardia, hypertension, mydriasis, diaphoresis, lacrimation, salivation, nausea, vomiting, and flushing can occur following intravenous administration. β-Adrenergic antagonists may attenuate some of the peripheral toxicity but may also result in unopposed α_1-adrenergic activity and worsening of hypertension, and should be avoided. Benzodiazepine administration may be sufficient for the treatment of agitation and sympathomimetic effects related to yohimbine.

Apomorphine Sublingual apomorphine effects erection through activation of central dopaminergic pathways, most likely D_2 receptors in the paraventricular nucleus of the hypothalamus. Common adverse effects are nausea, headache, dizziness, and syncope.

Priapism

Priapism is defined as a prolonged involuntary erection, which is painful, unassociated with sexual stimulation, caused by inflow of blood to the penis in excess of outflow and can result in impotence. The corpora cavernosa become firm and the corpus spongiosum flaccid. Intracavernosal pressures can exceed arterial systolic pressure, resulting in cell death. Priapism can occur from an imbalance in neural stimuli, interference with venous outflow, or as a result of xenobiotic-induced inhibition of penile detumescence. Table 28–3 lists xenobiotics associated with priapism.

The goal in the treatment of priapism is detumescence with retention of potency. Initial therapy includes sedation with benzodiazepines, analgesia with opioids, and ice packs, and early urologic consultation. Oral terbutaline (5–10 mg) may be effective for xenobiotic-induced priapism. Aspiration and normal saline irrigation of the corpora cavernosa may be required. An α-adrenergic agonist (0.02 mg norepinephrine or 0.2 mg phenylephrine) diluted with

TABLE 28–3. Xenobiotics Associated with Priapism

Androgens	Cantharidin
Anticoagulants	Cocaine
Antihypertensives	Benzodiazepines
Guanethidine	Ethanol
Hydralazine	Marijuana
Labetalol	Papaverine
Phentolamine	Phosphodiesterase 5 inhibitors
Prazosin	Trazodone
Antipsychotics	

normal saline to 10-mL volume can be instilled by placing a 19-gauge butterfly needle into the corpora cavernosa. If the above measures fail, operative venous shunt placement may be required.

FEMALE FERTILITY

The female reproductive system consists of the female gonadal organs and the respective hormonal system. Female infertility may result from changes in hormone concentrations, direct toxicity to the ovum, interference with the transport of the ovum, or inhibition of implantation of the ovum in the uterus. Women usually notice reproductive abnormalities more quickly than men, because menses may be affected, although infertility may occur while normal menses persists.

Oogenesis

In contrast to men, women have a limited number of reproductive cells (ovarian follicles). Follicles are most numerous while the fetus is in utero, decreasing to approximately 2 million at birth. By the time a woman reaches puberty only 300,000–400,000 follicles are left, of which only about 400 will produce mature ova. In contrast, men produce millions of spermatozoa a day. Secretion of GnRH from the hypothalamus results in production of LH and FSH from the pituitary, which are required for ovarian follicle maturation. FSH induces early maturation by stimulating granulosa and thecal cell proliferation and estrogen production. LH is required for ovulation and for the formation of the corpus luteum. The corpus luteum continues estrogen production and produces progesterone, which stimulates the uterus to develop an endometrium receptive to any fertilized ovum. Table 28–1 lists xenobiotics that decrease female fertility.

Female Sexual Dysfunction

Female sexual dysfunction is classified into the following 4 categories: (a) sexual desire disorders, which include hypoactive sexual desire disorder and sexual aversion disorder; (b) sexual arousal disorder; (c) orgasmic disorder; and (d) sexual pain disorders, which include dyspareunia, vaginismus, and noncoital sexual pain disorder. The organic etiologies of female sexual dysfunction parallel that of male sexual and erectile dysfunction: vasculogenic, neurogenic, musculogenic, psychogenic, endocrinologic, and xenobiotic-induced causes.

Treatment for xenobiotic-induced female sexual dysfunction includes decreasing medication dosages, switching to alternate medications with less adverse effects on sexual function (eg, bupropion and nefazodone), temporary cessation of the medication (drug holiday), or adding another medication to stimulate sexual function. The majority of medical therapy for female sexual dysfunction is centered on hormonal therapy, both estrogen and androgen supplementation. Estrogen therapy is associated with a higher incidence of coronary disease, breast cancer, stroke, and venous thromboembolism.

ABORTIFACIENTS

An abortifacient is defined as an xenobiotic that affects early embryonic gestation to induce abortion. These substances may act by flushing the zygote from the fallopian tube, blocking the uterine horn, inhibiting implantation, in-

ducing fetal resorption, or by producing oxytocin-like activity that results in uterine irritation and contraction. Abortifacients may also indirectly affect pregnancy by altering hormonal levels through placental inhibition of human chorionic gonadotropin (hCG) or progesterone production, or through interference with progesterone receptors. Table 28–4 lists common abortifacients and their toxicity.

TOXICITY OF APHRODISIACS

Aphrodisiacs are defined as xenobiotics that heighten sexual desire, pleasure, and/or performance, and include agents from the plant, animal, and mineral kingdoms. Some "aphrodisiacs" in Asian countries contain lead and are associated with toxicity. Traditionally, aphrodisiacs from the Indian subcontinent con-

TABLE 28–4. Xenobiotics Used as Abortifacients

Xenobiotic	Source	Country of Origin or Use	Miscellaneous/ Toxicity
Bristly starbur—whole plant	*Acanthospermum hispidum*	Brazil	Preimplantation effects
α-Momorcharin (bitter melon)	*Momordica charantia*	China	Similar to trichosanthin
Pigeon pea—fresh leaves	*Cajanus cajan*	Brazil	Preimplantation effects
Devil's claw	*Ranunculus*	South Africa	Similar to pennyroyal oil
Chinese angelica	*Angelica polymorpha*	—	Anticoagulant effects, photodermatitis
Ergotamines	*Claviceps purpurea*	—	Oxytocic
Justica adhatoda	*Adhatoda vasica*	India	100% abortifacient in rats
Lagenaria breviflora Robert	*Lagenaria breviflora* Robert	Nigeria	Antiimplantation, oxytocic
Lysol disinfectant	—	—	Death after intrauterine administration
Methotrexate	—	—	Medical use
Methylcytosine (Blue cohosh)	*Caulophyllum thalictroides*	—	Toxicity similar to nicotine
Horseradish tree	*Moringa oleifera*	India	100% abortifacient in rats
Prostaglandin E analog	Misoprostol	Brazil, US	Marketed as Cytotec for gastric ulcers
Pulegone (Pennyroyal oil)	*Hedeoma pulegioides*	—	Hepatotoxicity; *N*-acetylcysteine (NAC) may be effective
Quinine	Cinchona bark	—	Antimalarial
Rue	*Ruta graveolens*	Mexico	Preimplantation effects and oxytocic in animals
RU-486	Mifepristone	France, US	Marketed as an emergency contraceptive; administered with prostaglandins
Trichosanthin (compound Q) (snake gourd)	*Trichosanthes kirilowii*	China	Inhibits protein synthesis, ↓ hCG, ↓ progesterone

tain silver and/or gold, but occasionally lead is substituted. The indications for chelation therapy are the same as in other cases of lead poisoning (Chap. 91).

Topical Xenobiotics

Spanish Fly

Spanish fly is cantharidin derived from crushed blister beetles (*Cantharis vesicatoria*) and is used to enhance sexual potency. Adverse effects are a consequence of the vesicant properties, resulting in gastrointestinal, dermatologic, genitourinary, renal, cardiac, pulmonary, neurologic, and hematologic effects. Symptoms generally occur 2–6 hours after ingestion. Gastrointestinal and genitourinary signs include dysuria, oral pain, dysphagia, nausea, hematemesis, and hematuria. Blistering of mucous membranes also occurs, and patients commonly develop hemorrhagic mucositis of the mouth, esophagus, and stomach. Fatal gastrointestinal hemorrhage has been reported, and the lethal dose varies from 10–80 mg in adults. Patients may also develop dysrhythmias, ST-segment elevation, T-wave changes, acute lung injury, and bronchial bronchialar hemorrhage.

Bufotoxin

"Stone," "love stone," "black stone," and "rock hard" all refer to topical aphrodisiac preparations made from dried toad venom that contains bufalin, cinobufalin, cinobufagin, and other cardioactive steroids in the bufadienolide class that have a similar structure and action to digoxin. Digoxin immunoassay may be positive after exposure to these xenobiotics, although the concentration may not correlate with toxicity. One patient was successfully treated with digoxin-specific Fab fragments (Chap. 62 and Antidotes in Brief: Digoxin-Specific Antibody Fragments [Fab]).

Inhaled Xenobiotics

Nitrites

Alkyl (amyl, butyl, and isobutyl) nitrites are aliphatic esters of nitrous acid and are yellow, highly volatile, sweet-smelling liquids administered by inhalation. Amyl nitrite and other alkyl nitrites are especially popular aphrodisiacs among men who have sex with other men. They are inhaled during foreplay to obtain a "high" and to produce anal sphincter relaxation, or just before orgasm to heighten and prolong the climax. The relaxation of vascular smooth muscle also results in potent vasodilation and hypotension. Blood pressure can decrease significantly within 30 seconds of inhalation. Inhalation of as little as 5 drops can result in hy-

TABLE 28–5. Xenobiotics That Cause Incontinence and Retention

Xenobiotic	Action
α-Adrenergic agonists	Increase internal sphincter tone; retention
α-Adrenergic antagonists	Decrease internal sphincter tone
Anticholinergics	Impair detrusor contraction; retention
Calcium channel blockers	Decrease detrusor contraction
Diuretics	Overflow (volume increase)
Opioids	Impair detrusor contraction; retention
Sedatives-hypnotics	Decrease sensorium; retention

Reprinted with permission from Chutka DS, Fleming KC, Evans MP, et al: Urinary incontinence in the elderly population. Mayo Clin Proc 1996;71:93–101.

TABLE 28–6. Xenobiotics That Cause Colored Urine

Milky
- Chyle
- Lipids
- Pyuria

Reddish brown
- Anthraquinone
- Bilirubin
- Chloroquine
- Ibuprofen
- Levodopa
- Methyldopa
- Phenacetin
- Phenazopyridine
- Phenothiazines
- Phenytoin
- Porphyrins
- Trinitrophenol

Reddish-orange
- Aminopyrine
- Aniline dyes
- Antipyrine
- Chlorzoxazone
- Doxorubicin
- Ibuprofen
- Mannose
- Phenacetin
- Phenazopyridine
- Phenothiazines
- Phenytoin
- Rifampin
- Salicylazosulfapyridine

Red
- Anthraquinones
- Beets
- Blackberries
- Eosin
- Erythrocytes
- Hemoglobin
- Myoglobin
- Porphyrins
- Rhubarb

Yellow-brown
- Aloe
- Anthraquinones
- Chloroquine
- Fava beans
- Nitrofurantoin
- Primaquine
- Rhubarb
- Sulfamethoxazole

Yellow
- Fluorescein
- Phenacetin
- Quinacrine
- Riboflavin
- Santonin

Yellow orange
- Aminopyrine
- Anisindione
- Carrots
- Sulfasalazine
- Vitamin A
- Warfarin

Black
- Alcaptonuria
- Homogentisic acid
- Melanin
- *p*-Hydroxyphenylpyruvic acid

Brown-black
- Cascara
- Iron
- Methyldopa
- Phenylhydrazine
- Senna

Greenish-blue
- Amitriptyline
- Anthraquinones
- Biliverdin
- Chlorophyll breath mints
- Flavin derivatives
- Food dye and color blue no. 1
- Indicans
- Indigo blue
- Magnesium salicylate
- Methylene blue
- Phenol
- Thymol

potension and reflex tachycardia. Headache, nausea, and syncope are also common. Nitrites can also cause methemoglobinemia (Chap. 122).

URINARY SYSTEM

The urinary system is composed of the kidneys, ureters, bladder, and urethra. Many xenobiotics are concentrated by the kidneys and eliminated in the urine. The following discusses the effect of xenobiotics on the bladder and urine. Chapter 27 further discusses xenobiotics affecting the kidneys.

Bladder Anatomy and Physiology

The bladder is a hollow, muscular reservoir composed of two parts, the body and the neck, and normally stores 350–450 mL of urine in adults. A smooth muscle, the detrusor muscle, makes up the bulk of the body and contracts during urination. Urine from the ureters enters the bladder at the uppermost part of the trigone, an area in the posterior wall of the bladder, and leaves via the neck and the posterior urethra. Surrounding the neck and posterior urethra is smooth muscle interlaced with elastic tissue to form the internal sphincter. Sympathetic innervation from S2 to S4 of the sacral spinal cord to the internal sphincter maintains smooth muscle contraction. Distal to the internal sphincter is an area with voluntary skeletal muscle that forms the external sphincter.

Stimulation of α- and β-adrenergic receptors results in internal sphincter contraction, increased bladder outlet resistance, and bladder filling, leading to urinary retention. Parasympathetic pre- and postganglionic fibers release acetylcholine to M_2 and M_3 muscarinic receptors in the detrusor muscle. Stimulation of M_3 receptors is responsible for detrusor muscle contraction and bladder emptying. Conversely, anticholinergics prevent bladder emptying and result in urinary retention. There are many etiologies for urinary incontinence and retention, including various xenobiotic exposures (Table 28–5).

Abnormalities in Urinalysis

Abnormalities of the urinalysis are often useful in identifying xenobiotic exposures. Color change or the presence of crystals may aid in diagnosis. In 50% of cases, the urinalysis in patients who ingest ethylene glycol shows calcium oxalate or hippurate crystals. Crystalluria is also described after therapeutic doses of salicylate, phenacetin, sulfonamide, and quinolones. After large ingestions, crystals can be seen with methotrexate, amoxicillin, cephalexin, ampicillin, and indinavir. Urine color is dependent on several factors, including pH, concentration, natural pigments, and length of time exposed to air. Table 28–6 notes causes of colored urine.

29 Dermatologic Principles

The adult skin covers an average surface area of 2 m^2. Despite its outwardly simple structure and function, the skin is actually extraordinarily complex. For this reason, different xenobiotics may produce clinically similar skin changes and many xenobiotics may produce diverse dermal lesions.

SKIN ANATOMY AND PHYSIOLOGY

The skin has three main anatomic components: the epidermis, the dermis, and the subcutis or hypodermis. The primary physiologic role of the epidermis, the most external layer of the skin, is to maintain water homeostasis and to establish immunologic surveillance. Its outermost layer, the stratum corneum, or horny layer, is predominantly responsible for the protective function of the skin. The stratum corneum is covered by a surface film composed of sebum emulsified with sweat and breakdown products from the horny layer. Hydrocarbon solvents, such as gasoline or methanol, or detergents, commonly produce a "defatting dermatitis" by keratolysis or the dissolution of these surface lipids.

The other toxicologically important component of the skin is the arteriovenous framework, consisting of a deep plexus in the region of the subcutaneous dermal junction. Through these blood vessels, xenobiotics exposed to the skin can be transported internally. Nerve endings and apocrine, sebaceous, and eccrine (sweat) glands also are located in this dermal layer. Pilosebaceous follicles, which are present all over the body, consist of a hair shaft, hair follicle, sebaceous gland, sensory end organ, and erector pili. Certain halogenated aromatic chemicals, such as polychlorinated biphenyls (PCBs), dioxin, and 2,4-dichlorophenoxyacetic acid, cause hyperkeratosis of the follicular canal and result in chloracne.

TOPICAL TOXICITY

Exposure to a myriad of industrial or environmental xenobiotics may result in skin "burns." Although the majority of these xenobiotics injure the skin through chemical reactivity (eg, oxidation, corrosion, vesication) rather than thermal damage, the clinical appearances of both are often identical.

Acids penetrate into the subcutaneous tissue and form a thick, leathery eschar that limits their spread. The histopathologic finding following acid injury is termed *coagulative necrosis*. Alkali exposures characteristically produce a liquefactive necrosis, which allows continued penetration of the corrosive xenobiotic; consequently, dermal injury following alkali exposure is typically more severe than after an equivalent-magnitude acid exposure.

ABSORPTION

Lipid solubility is the most important factor determining dermal absorption, although concentration, duration of exposure, molecular weight, and specific skin characteristics are also important determinants. Thus, although metal ions such as Hg^+ have limited skin penetration, the addition of a methyl group, to form methylmercury, increases its lipophilicity and hence its systemic absorption. Dimethylmercury, formed by the addition of another methyl group, may produce life-

threatening systemic effects with only a single drop applied to the skin (Chap. 92). It is important to note that the nonionized component of the weakly acidic hydrofluoric (HF) acid is able to penetrate deeply through the skin and even bone.

The vehicle of a xenobiotic may also influence absorption and indeed transdermal drug delivery systems are based on their ability to alter the skin partition coefficient through the use of an optimized vehicle. Similarly, through localized dermal occlusion, transdermal systems hydrate the skin and raise its temperature to increase the permeability. Despite these techniques to enhance drug delivery, transdermal systems still require that large amounts of drug be present externally to maximize the transcutaneous gradient.

Percutaneous absorption may produce systemic, even life-threatening, toxicity. Morbidity and mortality are reported with the topical application of podophyllin, camphor, phenol, organic phosphorus insecticides, ethanol, organic chlorines, nitrates, or salicylic acid. Children are particularly at risk for toxicities from percutaneous absorption because their skin is more penetrable than that of an adult, and specific anatomic sites, such as the face, often represent larger percentage of body surface areas than in the adult. Furthermore, there is enhanced absorption on anatomic parts of the body with thinner skin, such as the mucous membranes, eyelids, and intertriginous areas (axillae, groin, inframammary, and intergluteal).

PRINCIPLES OF DERMAL DECONTAMINATION

Following contact with xenobiotics, the skin should be thoroughly cleansed to prevent direct effects and systemic absorption. In general, water in copious amounts is the decontamination fluid of choice for skin irrigation. Soap should be used when adherent xenobiotics are involved. Following exposures to airborne xenobiotics, the mouth, nasal cavities, eyes, and ear canals should also be irrigated with appropriate solutions such as water or 0.9% NaCl. For nonambulatory patients, the decontamination process may need to be conducted using special collection litters if available.

There are only a few situations in which water should not be used for skin decontamination. This includes contamination involving the reactive metallic forms of the alkali metals, sodium, potassium, lithium, cesium, and rubidium, which react with water to form strong bases. The dusts of pure magnesium, sulfur, strontium, titanium, uranium, yttrium, zinc, and zirconium will ignite or explode in contact with water. Thus, following exposure to these metals, any residual metal should be removed mechanically with forceps, gauze, or towels and stored in mineral oil. Phenol has a tendency to thicken and become difficult to remove following exposure to water. Suggestions for phenol decontamination include high-flow water or polyethylene glycol solution. Lime, or CaO, also thickens and forms $Ca(OH)_2$ following wetting.

DERMATOLOGIC SIGNS OF SYSTEMIC DISEASES

Cyanosis

Normal cutaneous and mucosal pigmentation is caused by several factors, one of which is the visualization of the capillary beds through the translucent dermis and epidermis. Cyanosis manifests as a blue or violaceous appearance of the skin and mucous membranes. It occurs when the light-absorbing characteristics of hemoglobin are altered either through hypoxia or by oxidation of its iron moiety to the ferric state to form methemoglobin (Chap. 122). The presence of the more deeply colored hemoglobin moiety within the dermal

plexus will result in cyanosis that is most pronounced on the skin surfaces with the least overlying tissue, such as the mucous membranes or fingernails.

Jaundice

Jaundice is typically a sign of hepatocellular failure or hemolysis and is caused by hyperbilirubinemia, a condition in which this yellow pigment deposits in the subcutaneous fat. A yellow discoloration of the skin can also occur in patients with hypercarotenemia, caused by an excessive consumption of either carrots or the vitamin A precursor carotene. True hyperbilirubinemia is differentiated from hypercarotenemia by the presence of scleral icterus in patients with the former, which is absent in the latter. In addition, the cutaneous discoloration seen in hypercarotenemia can be removed by wiping the skin with an alcohol swab. Lycopenemia, a similar entity to carotenemia, is caused by the excessive consumption of tomatoes. Also, topical exposure to dinitrophenol or picric acid, stains from cigarette use, or inhalation of lycopene produces localized yellow discoloration of the skin.

Urticarial Drug Reactions

Urticarial drug reactions are characterized by transient, pruritic, edematous, pink papules, or wheals that arise in the dermis, and which blanch on palpation and are frequently associated with central clearing. This reaction pattern is representative of a type I, or IgE-dependent, immune reaction and commonly occurs as part of anaphylaxis. Widespread urticaria may occur following systemic absorption of an allergen, or following a minimal localized exposure in patients highly sensitized to the allergen. Following limited exposure, a localized form of urticaria also may occur. Regardless of the specific clinical presentation, this reaction occurs when immunologic recognition occurs between IgE molecules and a putative antigen triggering the immediate degranulation of mast cells, which are distributed along the dermal blood vessels, nerves, and appendages. The release of histamine, complements C3a and C5a, and other vasoactive mediators results in leakage of fluid from dermal capillaries as their endothelial cells contract. This produces the characteristic urticarial lesions described above. Activation of the nearby sensory neurons produces pruritus. Nonimmunologically mediated mast cell degranulation producing an identical urticarial syndrome may also occur following exposure to various xenobiotics, including jellyfish and benzoic acid.

Pruritus is a common manifestation of urticarial reactions but it may also be of nonimmunologic origin. Patients with hepatocellular disease frequently suffer from pruritus, which is mediated by the release of bile acids. In addition, pruritus in patients with chronic liver disease and obstructive jaundice may be caused by central mechanisms, as suggested by elevated CNS opioid peptide levels. Pruritus may also be caused by topical exposure to the urticating hairs of tarantula spiders, spines of the stinging nettle plant (*Urtica* sp), or certain xenobiotics such as capsaicin.

Xenobiotics also may evoke a type III immune reaction that causes mast cells to degranulate. The cellular inflammatory response to released chemotactic factors leads to increased vascular permeability.

Flushing

Vasodilation of the dermal arterioles leads to flushing. Flushing may occur following autonomically mediated vasodilation, as occurs with stress, anger, and

exposure to heat, or it may be chemically induced by vasoactive xenobiotics. Those xenobiotics that cause histamine release through a type I hypersensitivity reaction are the most frequent cause of toxin-induced flush. Histamine poisoning itself, most frequently caused by the consumption of scombrotoxic fish, may cause flushing. Flushing after the consumption of ethanol is common in patients of Asian descent and is similar to that following ethanol consumption in patients exposed to disulfiram or similar xenobiotics (Chap. 77). The inability to efficiently metabolize acetaldehyde, the initial metabolite of ethanol, as well as its increased production, results in the characteristic syndrome of vomiting, headache, and flushing. Niacin causes flushing through an arachidonic acid–mediated pathway that may be inhibited by preingesting aspirin. Vancomycin causes a transient bright red flushing that is mediated by histamine. It occurs during and immediately after rapid infusion and is termed "red man syndrome."

Skin Moisture

Drug-induced diaphoresis, sweating, may be part of a physiologic response to heat generation or may be pharmacologically mediated following sympathomimetic xenobiotic use. The eccrine sweat glands are responsible for sweat production and are uniquely innervated by acetylcholine-containing neurons within the autonomic nervous system. Because the postsynaptic receptor on the eccrine glands is muscarinic, most muscarinic agonists are capable of stimulating sweat production. Sweat production most commonly occurs following exposure to cholinesterase-inhibiting insecticides, such as organic phosphorus compounds, but it may also occur with direct-acting muscarinic agonists such as pilocarpine. Alternatively, antimuscarinics, such as atropine or diphenhydramine, reduce sweating and produce dry skin.

COMMON CLINICAL DERMATOLOGIC SYNDROMES

The ability to describe lesions accurately is an important skill, as is the ability to recognize specific patterns in order to help clinicians approach the patient with a rash. Several cutaneous reaction patterns account for the majority of clinical presentations occurring in patients with xenobiotic-induced dermatotoxicity (Table 29–1).

Toxic Epidermal Necrolysis and Related Syndromes

Toxic epidermal necrolysis (TEN) is a rare, life-threatening dermatologic emergency and medications are causally implicated in 80–95% of cases. The cutaneous reaction pattern is characterized by tenderness and erythema of the skin and mucosa, followed by extensive cutaneous and mucosal exfoliation. Classically, the macular erythema occurs within days of the exposure to the implicated substance and is preceded by malaise, headache, fever, myalgias, arthralgias, nausea, vomiting, diarrhea, chest pain, or cough. The face, neck, and central trunk are usually the initial areas affected. The disease generally progresses to involve the extremities and the remainder of the body. Individual lesions are reminiscent of target lesions because of their dusky centers. The entire thickness of the epidermis, including the nails and the mucosa, becomes necrotic and may slough off. A Nikolsky sign, consisting of sloughing of the epidermis when direct pressure is exerted on the skin lesion, may occur. If the diagnosis is suspected, a biopsy should be performed and treatment

TABLE 29–1. Xenobiotics Commonly Associated with Various Cutaneous Reaction Patterns

Acneiform
- ACTH
- Amoxapine
- Androgens
- Azathioprine
- Bromides
- Corticosteroids
- Danazol
- Dantrolene
- Halogenated hydrocarbons
- Iodides
- Isoniazid
- Lithium
- Oral contraceptives
- Phenytoin

Alopecia
- Anticoagulants
- Chemotherapeutics
- Hormones
- NSAIDs
- Phenytoin
- Retinoids
- Selenium
- Thallium

Contact dermatitis
- Bacitracin
- Balsam of Peru
- Benzocaine
- Carba mix
- Catechol
- Cobalt
- Diazolidinyl urea
- Ethylenediamine dihydrochloride
- Formaldehyde
- Fragrance mix
- Imidazolidinyl urea
- Lanolin
- Methylchloroisothiazolinone/methylisothiazolinone
- Neomycin sulfate
- Nickel
- *p*-Tert-butylphenol formaldehyde resin
- *p*-Phenylenediamine
- Quaternium-15
- Rosin (colophony)
- Sesquiterpene lactones
- Thimerosal

Erythema multiforme
- Antibiotics
- Allopurinol
- Barbiturates
- Carbamazepine
- Cimetidine
- Codeine
- Ethinyl estradiol
- Furosemide
- Gold
- Glutethimide
- Ketoconazole
- Methaqualone
- NSAIDs
- Nitrogen mustard
- Phenolphthalein
- Phenothiazines
- Phenytoin
- Sulfonamides
- Thiazides

Fixed drug eruptions
- Acetaminophen
- Allopurinol
- Barbiturates
- Captopril
- Carbamazepine
- Chloral hydrate
- Chlordiazepoxide
- Chlorpromazine
- Erythromycin
- D-Penicillamine
- Fiorinal
- Gold
- Griseofulvin
- Lithium
- Phenacetin
- Phenolphthalein
- Methaqualone
- Metronidazole
- Minocycline
- Naproxen
- NSAIDs
- Oral contraceptives
- Salicylates
- Sulindac

Maculopapular reactions
- Antibiotics
- Anticonvulsants
- Antihypertensive agents
- NSAIDs

Photosensitivity reactions
- Amiodarone
- Benoxaprofen
- Chlorpromazine
- Ciprofloxacin
- Dacarbazine
- 5-Fluorouracil
- Furosemide
- Griseofulvin
- Hydrochlorothiazide
- Hematoporphyrin
- Levofloxacin
- Nalidixic acid
- Naproxen
- Piroxicam
- Psoralen
- Sulfanilamide
- Tetracyclines
- Tolbutamide
- Vinblastine

Photoirritant contact dermatitis
- Celery
- Dispense blue 35
- Eosin
- Fig
- Fragrance materials
- Lime
- Parsnip
- Pitch

Toxic epidermal necrolysis
- Allopurinol
- L-Asparaginase
- Amoxapine
- Bactrim
- Mithramycin
- Nitrofurantoin
- NSAIDs
- Penicillin
- Phenytoin
- Prazosin
- Pyrimethamine–sulfadoxine
- Streptomycin
- Sulfonamides
- Sulfasalazine

Vasculitis
- Allopurinol
- Cimetidine
- Gold
- Hydralazine
- Levamisole
- NSAIDs
- Penicillin

(continued)

TABLE 29–1. Xenobiotics Commonly Associated with Various Cutaneous Reaction Patterns *(continued)*

Vasculitis *(cont)*	Barbiturates	Griseofulvin
Phenytoin	Captopril	Penicillamine
Propylthiouracil	Carbon monoxide	Penicillin
Quinidine	Chemotherapeutic agents	Rifampin
		Sulfonamides
Vesiculobullous	Dipyridamole	
Amoxapine	Furosemide	

initiated immediately. Removal of the inciting xenobiotic and transfer to a burn center for sterile wound care are widely accepted initial management strategies. Although glucocorticoids are not generally recommended, there is emerging support for the use of immunosuppressive or immunomodulatory therapies such as intravenous immunoglobulins, cyclophosphamide, and cyclosporine. Reported mortality is as high as 30%, particularly in those patients with gastrointestinal and tracheobronchial involvement.

Toxic epidermal necrolysis is often considered to be the most severe manifestation of the spectrum of syndromes represented by erythema multiforme. Erythema multiforme is characterized by target-shaped, erythematous macules and patches on the palms and soles, as well as on the trunk and extremities. The Nikolsky sign is absent. The etiology of recurrent erythema multiforme minor appears to be predominantly associated with recurrent herpes simplex virus infections. The Stevens-Johnson syndrome is similarly considered to be an overlap reaction with erythema multiforme major when greater than 30% body surface area is involved.

Blistering Reactions

Xenobiotic-related cutaneous blistering reactions may be clinically indistinguishable from autoimmune blistering reactions, such as pemphigus vulgaris or bullous pemphigoid. A number of medications, many of which contain a "thiol group," such as penicillamine and captopril, can induce either pemphigus foliaceous, a superficial blistering disorder in which the blister is at the level of the stratum corneum, or pemphigus vulgaris, in which blistering occurs at the suprabasilar level (Fig. 29–1).

Bullous Drug Eruptions

Multiple, large, ill-defined, dull, purplish-livid patches sometimes accompanied by large flaccid blisters characterize these eruptions. Typical locations include acral extremities, genitals, and intertriginous sites, and the process may be confused with toxic epidermal necrolysis if widely confluent. However, bullous drug eruptions spare the patient's mucous membranes. This reaction pattern generally is not life-threatening. Common causes include angiotensin-converting enzyme inhibitors and a variety of antibiotics.

Drug-Induced Hypersensitivity Syndrome

The hypersensitivity syndromes are characterized by erythroderma and facial and periorbital edema, and are typically accompanied by high fever, elevated hepatic aminotransferases, lymphadenopathy, and peripheral eosinophilia. The syndrome typically occurs 2–7 weeks after starting therapy with an anticon-

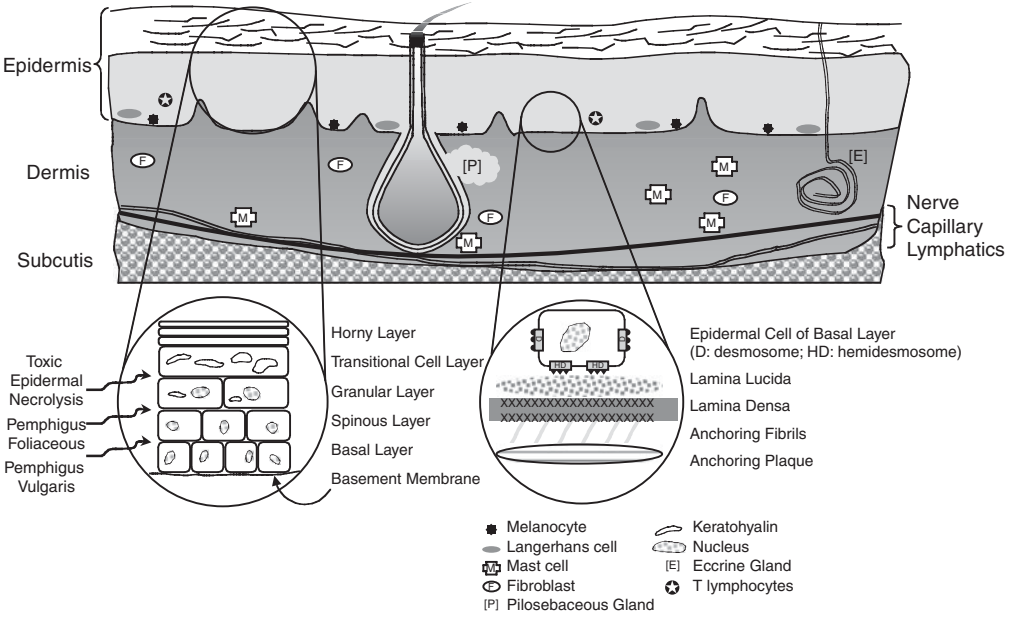

FIG. 29–1. Skin histology and pathology. Intraepidermal cleavage sites in various drug-induced blistering diseases. In pemphigus foliaceous, the cleavage is below or within granular layer, whereas in pemphigus vulgaris, it is suprabasilar. This accounts for the differing types of blisters found in the two diseases.

vulsant (Chap. 47) or sulfa-based drugs. Management of this syndrome is supportive following elimination of the offending substance.

Contact Dermatitis

When a xenobiotic contacts the skin, it can result in either an allergic contact dermatitis or an irritant dermatitis. Allergic contact dermatitis fits into the classic delayed hypersensitivity, or type IV immunologic reaction. The development of this reaction requires prior sensitization to an allergen, which, in most cases, acts as a hapten by binding with an endogenous molecule that is then presented to an appropriate immunologic T cell. Many allergens are associated with contact dermatitis. Among the most common sensitizers are chromates, urushiol (poison ivy), nickel, and neomycin.

Irritant dermatitis, although clinically indistinguishable, results from direct damage to the skin and does not require prior antigen sensitization. Irritant xenobiotics include acids, bases, solvents, and detergents, many of which, in their concentrated form or following prolonged exposure, can produce direct cellular injury.

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30 Reproductive and Perinatal Principles

One of the most dramatic effects of exposure to a xenobiotic during pregnancy is the birth of a child with congenital malformations. Teratology, the study of birth defects, principally has been concerned with the study of physical malformations. Only 4–6% of birth defects are related to known pharmaceuticals or occupational and environmental exposures (Table 30–1).

Female germ cells are formed in utero; adverse effects from xenobiotic exposure can theoretically occur from the time of a woman's own intrauterine development to the end of her reproductive years. Men generally receive less attention with respect to reproductive risks. Male gametes are formed after puberty; only from that time on are they susceptible to xenobiotic injury.

Xenobiotic exposures, including intentional overdose, before and during pregnancy can have effects throughout gestation and may extend into and beyond the newborn period. In addition, the effects of medication administration in the perinatal period and the special case of delivering xenobiotics to an infant via breast milk deserve special consideration.

PHYSIOLOGIC CHANGES DURING PREGNANCY THAT AFFECT DRUG DISTRIBUTION

During pregnancy there is delayed gastric emptying, decreased gastrointestinal (GI) motility, and increased transit time through the GI tract. These changes result in delayed but more complete GI absorption of xenobiotics and, consequently, lower peak plasma concentrations. An increased free xenobiotic concentration in the pregnant woman may be caused by several factors, such as decreased plasma albumin, increased binding competition, and decreased hepatic biotransformation during the later stages of pregnancy. Fat stores increase during the early stages of pregnancy; free fatty acids are released during the later stages and, with them, xenobiotics that may have accumulated in the lipid compartment. The increased concentration of free fatty acids can compete with circulating free xenobiotic for binding sites on albumin.

Early in pregnancy, increased fat stores, as well as the increased plasma and extracellular fluid volume, will lead to a greater volume of distribution. Increased renal blood flow and glomerular filtration may result in increased renal elimination.

Cardiac output increases throughout pregnancy, with the placenta receiving a gradually increasing proportion of total blood volume. Consequently, xenobiotic delivery to the placenta may increase over the course of pregnancy.

XENOBIOTIC EXPOSURE IN PREGNANT WOMEN

Between 30% and 80% of pregnant women take a xenobiotic sometime during pregnancy, primarily analgesics, antipyretics, antimicrobials, and anti-

TABLE 30–1. Known and Possible Human Teratogens

Amiodarone
Androgens (eg, methyltestosterone, danazol)
Alkylating agents (eg, nitrogen mustard)
Aminopterin, methotrexate (amethopterin)
Angiotensin-converting enzyme inhibitors (eg, enalapril)
Carbamazepine
Carbon monoxide
Cocaine
Corticosteroids
Coumadin
Diazepam and other benzodiazepines
Diethylstilbestrol (DES)
Ethanol
Fluconazole
Indomethacin
Iodine and iodine-containing products
Lead
Lithium carbonate
Methimazole
Methylmercury, mercuric sulfide
Methylene blue (intra-amniotic injection)
Misoprostol
Oxazolidine-2,4-diones (trimethadione, paramethadione)
Penicillamine
Phenytoin
Polychlorinated biphenyls
Progestins (eg, ethisterone, norethindrone)
Quinine
Radiation, ionizing
Retinoids (isotretinoin, etretinate, high-dose vitamin A)
Smoking
Streptomycin
Tetracycline
Thalidomide
Trimethoprim
Valproic acid
Vitamin D

Adapted from Brent RL: Environmental causes of human congenital malformations: The pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. Pediatrics 2004;113:957–968; Nulman I, Atanackovic G, Koren G: Teratogenic drugs and chemicals in humans. In: Koren G, ed: Maternal–Fetal Toxicology: A Clinician's Guide, 3rd ed. New York, Marcel Dekker, 2001; and Polifka JE, Friedman JM: Medical genetics: 1. Clinical teratology in the age of genomics. CMAJ 2002;167:265–273.

emetics, as well as vitamins, caffeine, ethanol, and smoking. Some pregnant women use medications to treat chronic disease; others use medications prior to recognizing that they are pregnant. Pharmaceutical manufacturers are required by law to label their products with respect to use in pregnancy according to standards promulgated by the US Food and Drug Administration (FDA) (Table 30–2).

Estimates of substance use in pregnancy vary tremendously depending on the geographic location, practice environment, patient population, and screen-

TABLE 30–2. FDA Use-in-Pregnancy Ratings[a]

Category	Risk to Human Fetus	Example(s)	Basis
A	No known risk	Vitamins	***Controlled studies show no risk.*** Adequate, well-controlled studies in pregnant women do not demonstrate a risk to the fetus and if animal studies exist, they do not demonstrate a risk.
B	Unlikely risk	Acetaminophen, penicillin	***No evidence of risk in humans.*** Either animal studies show risk but human studies do not, or if no adequate human studies have been done, animal studies show no risk.
C	Unknown risk	Albuterol	***Risk cannot be ruled out.*** Animal studies may or may not show risk, but human studies do not exist. However, benefits may justify the potential or unknown risk.
D	Known risk, but benefit may outweigh risk	Tetracycline	***Positive evidence of risk.*** Investigational or postmarketing data or human studies show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk; for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
X	Known risk but risk significantly outweighs benefit	Isotretinoin	***Contraindicated in pregnancy.*** Studies in animals or humans or investigational or postmarketing reports have shown fetal risk that clearly outweighs any possible benefit to the patient.

[a]Based on US Food and Drug Administration. Specific requirements on content and format of labeling for human prescription drugs. 21 CFR Ch. I (4–1–04 ed.) § 201.57.

ing method. Among a large national sample screened for xenobiotic use during pregnancy, 20% of pregnant women smoked, 20% drank ethanol, 3% used marijuana, 0.5% used cocaine, 0.1% used methadone, and fewer than 0.1% used heroin.

PLACENTAL REGULATION OF XENOBIOTIC TRANSFER TO THE FETUS

Most xenobiotics enter the fetal circulation by passive diffusion down a concentration gradient across the placental membranes. The characteristics of a substance that favor this passive diffusion are low molecular weight, lipid solubility, neutral polarity, and low protein binding. Polar molecules and ions may be transported through interstitial pores. Xenobiotics with a molecular weight greater than 1000 daltons (eg, heparin) do not diffuse passively across the placenta.

Fetal blood pH changes during gestation. Embryonic intracellular pH is high relative to the pregnant woman. During this developmental stage, weak acids (eg, valproic acid) will diffuse across the placenta to the embryo and remain there because of "ion trapping." Although ion trapping does not explain the mechanism of teratogenesis, it may explain how xenobiotics accumulate in an embryo. Late in gestation the fetal blood is 0.10–0.15 pH units more acidic than the mother's blood; this may permit weakly basic xenobiotics to concentrate in the fetus during this period.

The placenta contains xenobiotic-metabolizing enzymes capable of performing both phase I and phase II reactions (Chaps. 9 and 26). However, the concentration of biotransforming enzymes in the placenta is significantly lower than that in the liver, and it is unlikely that the level of enzymatic activity is protective for the fetus. Moreover, the fetus may be exposed to reactive intermediates that form during these processes.

EFFECTS OF XENOBIOTICS ON THE DEVELOPING ORGANISM

Teratogens generally behave according to a dose–response curve; there is a threshold dose below which no effects occur and as the dose of the teratogen increases above the threshold, the magnitude of the effect increases. The effects might be the number of offspring that die or suffer malformations or the extent or severity of malformations. Strictly, teratogenic effects are those that occur at doses that do not cause maternal toxicity because maternal toxicity itself might be responsible for an observed adverse or teratogenic effect on the developing organism.

Organogenesis occurs during the embryonic stage of development between days 18 and 60 of gestation. Most gross malformations are determined before day 36, although genitourinary and craniofacial anomalies occur later. The period of susceptibility to teratogenic effects varies for each organ system. For instance, the palate has a very short period of sensitivity, lasting approximately 3 weeks, whereas the central nervous system (CNS) remains susceptible throughout gestation.

Another concern during the fetal period is the initiation of carcinogenesis. Significant cellular replication and proliferation lead to a dramatic growth in size of the organism. At the same time, when the fetus is exposed to xenobiotics, development of biotransformation systems may expose the organism to reactive metabolites that might initiate tumor formation. Some tumors, such as neuroblastoma, appear early in postnatal life, suggesting a prenatal origin.

MANAGEMENT OF ACUTE POISONING IN THE PREGNANT WOMAN

Suicide and suicide attempts during pregnancy are uncommon. Each year a small number of women die during pregnancy or the postpartum period; 1–5% of these pregnancy-related deaths may be the result of suicide. Medication ingestion is a common method of attempting suicide during pregnancy. Analgesics, vitamins, iron, antibiotics, and psychotropic medications account for 50–79% of the reported ingestions by pregnant women.

Managing any acute overdose during pregnancy provokes discussion of several questions. Is the general management different? Is the fetus at risk of poisoning from a maternal overdose? Is there a teratogenic risk to the fetus from an acute overdose or poisoning? Is the use of an antidote contraindicated or should use be modified? When should termination of a pregnancy be recommended?

Although a single high-dose exposure to a xenobiotic during the period of organogenesis might seem analogous to an experimental model to induce teratogenesis, most xenobiotics ingested as a single acute overdose do not induce physical deformities. Ethanol teratogenicity may be related to binge drinking, but a single binge will probably not cause significant effects. It is very unlikely that the small risk of possible teratogenesis would ever lead to a recommendation for termination of pregnancy after an acute overdose of most xenobiotics.

In general, any condition that leads to a severe metabolic derangement in the pregnant woman is likely to have an adverse impact on the developing fetus. As a general approach, the management of overdose in a pregnant woman should follow the principles outlined in Chap. 4, with close attention paid to the airway, oxygenation, and hemodynamic stability.

Gastrointestinal decontamination is frequently a part of the early management of acute poisoning in the nonpregnant patient. Gastric lavage is not specifically contraindicated for the pregnant patient; the usual concerns about protecting the airway apply to the pregnant patient as well. Syrup of ipecac is no longer recommended as a standard therapy for the management of ingestions, although pregnancy was previously considered a relative contraindication to its use because vomiting increases both intrathoracic and intraabdominal pressure.

There is no specific contraindication to the use of activated charcoal in a pregnant woman. There may be a specific role for whole-bowel irrigation in the management of several xenobiotic exposures, particularly in the treatment of iron overdose in pregnancy (see below). The use of polyethylene glycol is generally safe in pregnant women.

In considering the use of antidotes, the primary concern should be for the health of the pregnant woman. Almost all antidotes are designated as FDA pregnancy-risk category C; that is, there is little specific information to guide their use. Ethanol is labeled as category D (positive evidence of risk), although this is presumably related to chronic use throughout pregnancy, not as an antidote. Fomepizole, which has replaced ethanol as the preferred antidote for toxic alcohol poisoning, is labeled as category C. *N*-acetylcysteine, glucagon, and naloxone are category B medications.

BREAST-FEEDING

Many women use prescription and nonprescription medications while breast-feeding and are concerned about the possible ill effects on the infant of these medications in the breast milk. This concern extends to the possible exposure of the infant to occupational and environmental xenobiotics via breast milk. The response to many of these concerns can be determined by the answer to the question: "Does the risk to an infant from a xenobiotic exposure via breast milk exceed the benefit of being breast-fed?"

Pharmacokinetic factors determine the amount of xenobiotic available for transfer from maternal plasma into breast milk; only free xenobiotic can traverse the mammary alveolar membrane. Most xenobiotics are transported by passive diffusion. The factors that determine how well a chemical diffuses across the membrane are similar to those for other biologic membranes, such as the placenta—molecular weight, lipid solubility, and degree of ionization.

The net effect of these physiologic and physicochemical processes is expressed in the milk-to-plasma (M/P) ratio. Xenobiotics with higher M/P ratios have relatively greater concentrations in breast milk. The M/P ratio does

not take into account differences in xenobiotic concentration that may result from (a) repeat or chronic dosing; (b) breast-feeding at different times relative to maternal medication dosing; (c) differences in milk production during the day or even during a particular breast-feeding session; (d) the time postpartum (days, weeks, or months) when the measurement is made; and (e) maternal disease.

Many xenobiotics, including pharmaceuticals, foods, and environmental agents, have been found in breast milk; Table 30–3 lists some of their effects.

TABLE 30–3. Selected Xenobiotics Associated with Effects on Some Nursing Infants

	Effect
Xenobiotic	Use with Caution
5-Aminosalicylic acid	Diarrhea
Acebutolol, atenolol, nadolol, sotalol, timolol	Hypotension, bradycardia, tachypnea, cyanosis
Amiodarone	Possible hypothyroidism
Aspirin	Metabolic acidosis; may affect platelet function; rash
Bromocriptine	Suppresses lactation
Chloramphenicol	Potential risk for aplastic anemia or gray-baby syndrome
Chlorpromazine	Galactorrhea in mother; drowsiness and lethargy in infant; decline in developmental scores
Cimetidine	Possible antiandrogenic effects
Clemastine	Drowsiness, irritability, refusal to feed, high-pitched cry, meningismus
Clofazimine	Possible increased skin pigmentation
Cyclophosphamide, cyclosporine, doxorubicin, methotrexate	Neutropenia, thrombocytopenia, possible immune suppression, unknown effect on growth or association with carcinogenesis
Ergotamine	Vomiting, diarrhea, seizures; may inhibit prolactin secretion and lactation
Fluoxetine	Colic, irritability, feeding and sleeping disorders, slow weight gain
Haloperidol	Decline in developmental scores
Lamotrigine	Potential therapeutic serum concentrations in infant
Lithium	Subtherapeutic concentrations in infant
Metronidazole, tinidazole	In vitro mutagen
Phenindione	Risk of hemorrhage
Phenobarbital	Sedation in exposed infants; withdrawal after weaning from phenobarbital-containing milk; methemoglobinemia
Primidone	Sedation, feeding problems
Sulfapyridine, sulfisoxazole	Caution in infant with jaundice or G6PD deficiency and in ill, stressed, or premature infant
Sulfasalazine	Bloody diarrhea
Tetracycline	May cause staining of infant teeth after prolonged maternal use
Thiouracil, methimazole	May cause thyroid suppression and goiter

Adapted with permission from American Academy of Pediatrics, Committee on Drugs: The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108:776–789.

TOXICOLOGIC PROBLEMS IN THE NEONATE

It is estimated that approximately 8% of all medication doses administered in neonatal intensive care units (NICU) may be up to 10 times greater than or one-tenth of the dose ordered. As many as 30% of newborns in NICUs may sustain adverse drug effects, some of which may be life-threatening or fatal.

GI absorption of xenobiotics in the neonate is generally slower than in adults. This delay may be related to decreased gastric acid secretion, decreased gastric emptying and transit time, and decreased pancreatic enzyme activity. Because of differences in total body water and fat compared to the adult, the distribution of absorbed xenobiotics may differ in neonates. Water represents 80% of body weight in a full-term baby compared to 60% in an adult. Approximately 20% of a term baby's body weight is fat, compared to only 3% in a premature baby. The increased volume of water means that the volume of distribution for some water-soluble xenobiotics, such as theophylline and phenobarbital, is increased.

Protein binding of xenobiotics is reduced in newborns compared to adults: the serum concentration of proteins is lower, there are fewer receptor sites that become saturated at lower xenobiotic concentrations, and binding sites have decreased binding affinity. Newborn infants have decreased or altered hepatic metabolic capacity compared to adults, which may lead to xenobiotic toxicity. In addition, immaturity of the cytochrome P450 system leads to increased elimination half-lives of xenobiotics such as phenytoin, phenobarbital, and theophylline.

Two syndromes related to immature metabolic function are described. The "gasping-baby syndrome," which is characterized by gasping respirations, metabolic acidosis, hypotension, CNS depression, and occasionally death, is attributed to benzyl alcohol, a bacteriostatic agent added to intravenous flush solutions. Immature glucuronidation in the neonate is responsible for the "gray-baby syndrome" following high doses of chloramphenicol (Chaps. 45 and 31).

31 Pediatric Principles

Although the basic approach to the medical management of toxicologic problems outlined in Chap. 4 is generally applicable to both children and adults, there are issues, such as abuse by poisoning, that are of particular concern to children. This chapter provides a pediatric perspective on the application of toxicologic principles.

The American Association of Poison Control Centers (AAPCC) reports approximately 1.5 million potentially toxic exposures per year for children and adolescents ages 0–19 years, and these pediatric exposures represent 67% of the reported exposures for all age groups. Children younger than age 6 years account for 53% of all reported pediatric and adult poisoning exposures. Children younger than age 6 years account for 79% of all reported pediatric exposures; children 6–12 years old account for 10%, and adolescents 13–19 years old account for 11%. Approximately 11,000 exposures each year are classified as adverse drug reactions. These account for 0.3% of exposures in young children, and 2% of exposures in older children and adolescents. Approximately 56% of pediatric exposures are to xenobiotics that are commonly found around the house, such as cleaning agents, cosmetics, plants, hydrocarbons, and insecticides; whereas approximately 44% are to pharmaceuticals.

Several characteristics associated with ingestions in toddlers differentiate them from ingestions in adolescents or adults: (a) they are without suicidal intent; (b) there is usually only one xenobiotic involved; (c) the xenobiotics are usually nontoxic; (d) the amount is usually small; and (e) toddlers usually present for evaluation within an hour after the ingestion or soon after the ingestion is discovered.

The peak age for childhood poisoning is between 1 and 3 years. Unintentional ingestion is unusual after age 5 years and between the ages of 5 and 9 years, poisoning may be a reflection of intrafamilial stress or suicidal intent. After age 9 years and through adolescence, overdose or poisoning frequently results either from a suicidal gesture or attempt or from an adverse effect while seeking drug-induced euphoria.

Because many children are exposed to nontoxic xenobiotics or to nontoxic amounts of toxic xenobiotics, it is not surprising that the relative number of children and adolescents who suffer significant morbidity is small.

Poison-related deaths represent approximately 2.5% of annual childhood and adolescent deaths from unintentional injury. The AAPCC reported 508 deaths in children younger than 6 years of age from 1983–2003, an average of about 24 deaths per year.

BEHAVIORAL, ENVIRONMENTAL, AND PHYSICAL ISSUES

Childhood and adolescence are times of tremendous growth and development. Some of these physical and social changes place children and teenagers at increased risk for poisonings. By 7 months of age an infant sitting up can pivot to grab an object; by 9–10 months of age most infants can creep and crawl; by 15 months of age most toddlers are walking quite competently and eagerly exploring. Between 9 and 12 months of age a child is developing a skillful pincer grasp with the thumb and forefinger that allows the child to pick up small objects. Throughout this period, one of the child's primary sensory experiences is sucking on or gumming objects that are placed in the

mouth. Thus, the combination of three developmental skills—the ability to move around the home and go beyond the immediate view of a guardian, the ability to pick up and manipulate small objects, and the tendency of children to put things in their mouths—places them at risk for both foreign-body aspiration and poisoning.

As children develop socially, they desire to become more like their parents, and they tend to imitate behaviors, such as taking medicine or using mouthwash. Children are taught that medicine is good for them when they are sick. Many children's medicines are sweetened and flavored to make them more palatable; in fact, many parents inappropriately encourage their children to take medicines by telling them "it tastes like candy." Children have been observed "making tea" from plants or "making pizza" with mushrooms from the yard.

It may be possible to reduce the likelihood of ingestion by making a xenobiotic unpalatable. Denatonium benzoate (Bitrex), an aversive bittering agent, is added to some liquid chemicals such as windshield washer fluid or antifreeze, with the expectation that this will prevent unintentional poisoning. Some trials have shown that older children respond negatively to these agents, but that younger children may ingest 1–2 teaspoonfuls of a xenobiotic before responding to the bitter flavor. This is an important consideration, because even this small an amount of a xenobiotic such as methanol may be toxic The actual usefulness of the bittering agent denatonium benzoate in poison prevention is largely unstudied.

The problem of unintentional ingestions is compounded by poison "look-alikes," xenobiotics that resemble candy or food products. Some common examples are ferrous sulfate tablets that look like M&M candies, prenatal vitamins that resemble Good and Plenty candies, and fuel oils that come in cans that resemble soft-drink containers.

Probably the most significant change to the physical aspect of the agent has been packaging of pharmaceuticals and some other xenobiotics with child-resistant closures as mandated by the Poison Prevention Packaging Act of 1972 (Chap. 130). This legislation is credited with a significant reduction in morbidity and mortality related to poisoning from aspirin and other regulated products, although this analysis has been challenged. Although child-resistant containers are a significant deterrent to unintentional ingestions in toddlers, they are not completely effective, and even without the problems noted, some children can open them.

Approximately 80% of pharmaceutical ingestions by children occur at home; the remainder occur at the homes of grandparents, other relatives, and friends. The medicine usually belongs either to the child or to the mother, although a significant number of medications, both at home and away from home, belong to a grandparent. Grandparents, other relatives, and family friends without children at home may not receive or keep medications in child-resistant containers and may not be attentive to safe-storage practices.

One important caveat relates to the storage of nonpharmaceutical xenobiotics, particularly those in liquid form, such as pesticides, hydrocarbons, and sodium hydroxide. These types of xenobiotics should never be transferred to familiar household containers such as food jars or wine or soda bottles for storage. Both children and adults have been exposed to poisons such as sodium hydroxide or potassium cyanide stored in bottles in the refrigerator.

GASTROINTESTINAL DECONTAMINATION

Chapter 8 is devoted to a complete discussion of gastrointestinal decontamination. This section reiterates and emphasizes only a few important points.

Orogastric lavage is often the preferred method of gastric emptying when indicated for most serious ingestions. Small children can generally tolerate orogastric lavage with a large-bore 28-French or 34-French tube; however, the smaller "large-bore" tubes may not be effective for removing large pills or fragments from the stomach of a small child. Placement of an orogastric tube is an unpleasant and frightening procedure for an infant or small child. There is often some local trauma related to tube placement and, rarely, there can be more serious injury, such as esophageal perforation. Also, many children vomit during placement of an orogastric tube. The use of orogastric lavage should be limited to cases in which the risk of serious poisoning is high, in which the likelihood of benefit is at least moderate, and in which the likely risk of injury to the child is small. This procedure should never be used as a form of punishment. To use orogastric lavage safely in a child with a diminished gag reflex or depressed level of consciousness, the trachea should be intubated to protect the airway.

Activated charcoal is one of the current mainstays of poison treatment. Children generally will not drink activated charcoal willingly. Some children can be coaxed to do so if the activated charcoal is disguised in a baby bottle or soft-drink container, or sweetened with juice or sorbitol. A nasogastric or orogastric tube may have to be inserted to administer activated charcoal. This can be a small-bore tube because it is not intended for lavage, although the smaller the bore, the more difficult it is to administer the thick slurry of activated charcoal. Placement of the tube, the presence of activated charcoal in the stomach, the effects of the xenobiotic, or the previous use of an emetic may all make the child vomit, making aspiration of activated charcoal or stomach contents a risk. For activated charcoal to be used safely in a patient who is comatose or who does not have a gag reflex, the trachea should be intubated and the airway protected. Even activated charcoal alone is unnecessary for a nontoxic ingestion.

METHODS OF ENHANCED ELIMINATION

For consequential poisoning with toxins such as methanol, ethylene glycol, salicylates, lithium, and theophylline, either hemodialysis or charcoal hemoperfusion is the optimal technique to enhance elimination, depending on the particular xenobiotic. These techniques can be performed on newborns or small infants in specially equipped centers with dedicated personnel. The primary limiting factor is the ability to obtain vascular access.

Exchange transfusion is a technique that is occasionally used to enhance drug elimination. This technique might be useful when multiple-dose activated charcoal cannot be administered, the xenobiotic is poorly adsorbed to charcoal, or access to specialized pediatric hemodialysis or hemoperfusion is not readily available.

XENOBIOTICS THAT MAY BE TOXIC OR FATAL IN SMALL QUANTITIES

When children ingest small quantities of toxic xenobiotics, they potentially ingest large doses relative to their small size. There are a number of xenobiotics that may cause significant toxicity or even death with as little as 1 pill or 1 teaspoonful. Table 31–1 lists some of these xenobiotics.

XENOBIOTICS THAT MAY HAVE DELAYED TOXICITY IN CHILDREN

There are several xenobiotics that warrant particular concern because their effects may be significantly delayed. Classic examples include atropine-diphenox-

TABLE 31–1. Xenobiotics That Can Cause Severe Toxicity to an Infant after a Small Dose

Antidiabetics (sulfonylureas)
Antihistamines
Benzocaine
β-Adrenergic antagonists (sustained-release)
Calcium channel blockers (sustained-release)
Camphor
Clonidine
Diphenoxylate-atropine (Lomotil)
Methanol/ethylene glycol
Methylsalicylate
Monoamine oxidase inhibitors
Opioids (methadone, codeine, OxyContin)
Phenothiazines
Quinine/chloroquine
Theophylline
Tricyclic antidepressants

ylate (Lomotil), sulfonylurens (such as glipizide), and slow-release formulations of many medications, such as calcium channel blockers.

XENOBIOTICS THAT HAVE UNUSUAL OR IDIOSYNCRATIC REACTIONS IN CHILDREN

Imidazolines/Clonidine: CNS Effects

Imidazoline medications such as tetrahydrozoline, oxymetazoline, xylometazoline, and naphazoline are nonprescription sympathomimetics used as nasal decongestants and conjunctival vasoconstrictors (Chap. 50). Clonidine is an imidazoline derivative used as an antihypertensive and for opioid withdrawal (Chap. 60). In small children, these medications can cause CNS depression, respiratory depression, bradycardia, miosis, and hypotension. The presumed mechanism of action is through stimulation of central α_2-adrenergic and imidazole receptors. Although naloxone has been reported to reverse some of the CNS effects of clonidine, we are not aware of any reports of its successful use with the other imidazolines (Chap. 60).

Ethanol: Hypoglycemia

Ethanol is the primary component of alcoholic beverages, as well as a major constituent of many liquid preparations, such as mouthwash, vanilla flavoring, and perfume. Besides the well-known sedative-hypnotic effects, ethanol intoxication in children is associated with hypoglycemia. Hypoglycemia results from the inhibition of gluconeogenesis in the setting of alcohol intoxication. There does not seem to be a blood alcohol concentration threshold for the development of hypoglycemia (Chap. 48 and 75).

MEDICATION ERRORS

Ever since the publication of the Institute of Medicine's report in 1999, increasing attention has been paid to the issue of medical errors in medicine. Although most of the research regarding medication errors has focused on adults (Chap. 134), this problem also affects children. Subsequent remarks in this section are generally limited to the pediatric literature.

In the 2003 AAPCC report, there were approximately 115,000 poison center calls related to therapeutic errors in children and adolescents, or approximately 7% of all calls; 1139, or approximately 2%, of these errors are described as "iatrogenic." During a recent AAPCC report, there were 34 deaths attributed to therapeutic errors, representing 7% of all deaths in children and adolescents. Although only 5% of the reported calls about young children were related to therapeutic errors, approximately 19% of the reported deaths were related to therapeutic errors. This is in contrast to adolescents for whom 9% of the calls, but only 2% of the reported deaths, were related to therapeutic errors.

INTENTIONAL POISONING AND CHILD ABUSE

Intentional poisoning of children is an unusual, although significant, form of child abuse. There are several types of intentional poisoning, some of which define pathologic characteristics of the caretaker: (a) undifferentiated child abuse, neglect, or impulsive acts under stress; (b) factitious illness (Münchhausen syndrome by proxy); (c) overt parental psychosis; (d) altruistic motivation or bizarre childrearing practices; and (e) the Medea complex, or the vengeful killing of a child out of spite for one's spouse.

Intentional poisoning is rarely suspected unless the patient dies and an autopsy is performed, a wide-ranging drug screen is ordered, or the history is bizarre enough to raise suspicions. In many cases where children were later found to be poisoned, the initial diagnoses were sepsis, meningitis, seizures, intracranial hemorrhage, gastroenteritis, apnea, apparent life-threatening events, or metabolic derangements. In addition to many pharmaceutical agents, salt, pepper, water, caffeine, ethylene glycol, herbs, plants, and traditional remedies have been used to poison children. Although the death rate from unintentional poisoning in childhood is much less than 1%, the death rate from inflicted poisoning may be as high as 20–30%. Intentional poisoning may be associated with other abuse; approximately 20% of poisoned children may have evidence of physical abuse.

Factitious illness (Münchhausen syndrome by proxy [MSBP]) is a condition in which a parent, usually the mother, fabricates a history of a nonexistent disease in a child or creates the signs and symptoms of disease in a child. This is usually a manifestation of the parent's complex psychiatric illness, which may include Münchhausen syndrome itself. There may be only a fine line separating MSBP from an intentional poisoning with intent to harm or kill a child. Regardless of the specific intent, this condition is considered a form of child abuse. Several warning signals may suggest a diagnosis of MSBP (Table 31–2).

Child abuse or neglect is part of the differential diagnosis in any case of childhood poisoning. Intentional poisoning should be considered for (a) an "ingestion" in a child younger than 1 year of age; (b) a case with a confusing history or presentation; (c) a child with a previous poisoning or whose siblings have been previously evaluated for poisoning; (d) a child with a previous presentation for a rare or unexplained medical condition; (e) a child with apnea, unexplained seizures, or an apparent life-threatening event; (f) a massive ingestion by a small child; (g) an ingestion of multiple xenobiotics by a small child; (h) an exposure to substances of abuse; (i) an intoxication with a xenobiotic to which a child could or would not have access; (j) "accidental ingestions" in the school-age child; (k) a history of previous trauma, child

TABLE 31–2. Factitious Illness (Münchhausen Syndrome by Proxy): Suggestive Characteristics in Clinical Situations

1. A persistent or recurrent illness that cannot be explained.
2. The history of disease or results of diagnostic tests are inconsistent with the general health and appearance of the child.
3. The signs and symptoms cause the clinician to remark, "I've never seen anything like this before!"
4. The signs and symptoms do not occur when the child is separated from the parent.
5. The parent is particularly attentive and refuses to leave the child's bedside, even for a few minutes.
6. The parent develops particularly close relations with hospital staff.
7. The parent seems less worried than the physician about the child's condition.
8. Treatments are not tolerated—intravenous lines fall out frequently, prescribed medications lead to vomiting.
9. The proposed diagnosis is a rare disease.
10. "Seizures" are unwitnessed by medical staff and reportedly do not respond to any treatment.
11. The parent has a complicated medical or psychiatric history.
12. The parent is or was associated with the healthcare field.

Adapted with permission from Meadow R: Münchhausen syndrome by proxy. Arch Dis Child 1982;57:92–98.

abuse, or neglect; and (l) sudden infant death syndrome or an unexplained death. These considerations of child abuse notwithstanding, rare diseases do occur. One child's rare inherited metabolic disorder, methyl malonic acidemia, was misdiagnosed as ethylene glycol poisoning because the chromatographic appearance of the metabolite propionic acid was similar to that of ethylene glycol.

32 Geriatric Principles

The population in developed countries is aging steadily. In the United States, those older than 65 years of age comprise not only an increasing proportion of the population at large (12%), but an increasing proportion of patients seen in medical practices. Patients older than 65 years of age account for 43% of emergency department visits and 48% of all critical care admissions from emergency departments. Although the elderly account for only a small minority of toxicologic exposures, once exposed they have the highest mortality rate. Among exposures reported to poison control centers in 2003, the fatality ratio (number of cases divided by number of deaths) increased with age and was highest among people 80 years of age and older. Table 32–1 lists the drugs most commonly responsible for toxicity in the elderly.

The presentation of drug toxicity may be delayed in the elderly and the presenting signs and symptoms may be atypical (eg, falls).

SUICIDE AND INTENTIONAL POISONINGS

The risk of suicide by all methods increases steadily with age, particularly among white men. The male-to-female ratio of suicide attempts narrows with increasing age, so that in the oldest age groups, men attempt suicide slightly more often than women, when all methods of attempted suicide are considered (Chap. 18).

In the United States, drug overdose accounts for only 3% of completed suicides in older men; among women, drug overdose is nearly as frequent a cause of death as firearms, each accounting for approximately 25% of successful suicides. When death by inhalation is included, poison exposure surpasses gunshot wounds as a cause of death among elderly women.

UNINTENTIONAL POISONING AND ADVERSE DRUG EVENTS

An adverse drug event (ADE) is defined as "an injury resulting from medical intervention related to a drug." This definition encompasses events that result from both inappropriate use of medications, such as a prescribing error, as well as from appropriate use. It may be challenging for the clinician to distinguish poisoning from ADEs in the elderly. Compared to younger adults, the elderly are at increased risk of unintentional poisoning, as well as other drug events. Although reported poisoning exposures among the elderly are much less frequent than among other age groups, the incidence of ADEs increases steadily with age. Moreover, when they occur, they are more likely to be serious. Serious ADEs, defined as those resulting in death, hospitalization, prolongation of hospitalization, or permanent or serious disability, are most prevalent among people 85 years of age and older.

SUBSTANCES OF ABUSE IN THE ELDERLY

Substance abuse declines with age but is important to consider in relevant clinical circumstances. Alcohol is the most common substance of abuse in people older than 65 years of age. Abuse of alcohol or other xenobiotics may be a continuation of long-term habits, but some older adults may first begin to use and abuse drugs in their 60s and 70s.

TABLE 32–1. Drugs Most Commonly Responsible for Toxicity in the Elderly[a]

Anticholinergics
Anticoagulants
Antidepressants
Antipsychotics
Cardiovascular medications
β-Adrenergic antagonists
Calcium channel blockers
Digoxin
Magnesium-containing antacids
Magnesium- and phosphate-containing laxatives
Nonsteroidal antiinflammatory drugs
Opioids
Salicylates
Sedative-hypnotics

[a]Polypharmacy increases toxicity as a result of diverse drug–drug interactions.

PHARMACOKINETICS

Age-related pharmacokinetic changes occur in the elderly (Table 32–2). The most important and consistent pharmacokinetic change that occurs with aging is a decrease in renal function. Glomerular filtration rate (GFR) declines, on the average, by 50% between the ages of 30 and 80 years. The GFR cannot be accurately predicted by serum creatinine because muscle mass, the source of serum creatinine, declines with age; consequently, in late life, serum creatinine

TABLE 32–2. Pharmacokinetic Considerations in the Elderly

	Young	Elderly	Consideration
Fat (% of body weight)	15	30 (↑)	↑ Vd for drugs distributing to fat (amitriptyline, diazepam)
Intracellular water (% of body weight)	42	30 (↓)	↓ Vd for water-soluble drugs
Muscle (% of body weight)	17	12 (↓)	↓ Vd for drugs distributing into lean tissue (acetaminophen, caffeine, digoxin, ethanol)
Albumin (g/dL)	4	↓ With acute or chronic illness	↑ Free levels of drugs if >90% bound to albumin, especially in overdose; interpretation of serum concentration altered
Liver	Normal	↓ Size ↓ Hepatic blood flow	Liver enzymes not predictive; drugs with high extraction may increase (propranolol, triazolam)
Kidney	Normal	↓ Renal blood flow ↓ GFR ↓ Tubular secretion	Accumulation (lithium, aminoglycosides, *N*-acetyl procainamide, ACE inhibitors, cimetidine, digoxin

Modified with permission from Mayersohn M: Special pharmacokinetic considerations in the elderly. In: Evans WE, Schentag JJ, Justo WJ, eds: Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring, 3rd ed. Vancouver, WA, Applied Therapeutics, 1992, pp. 1–43; and Fox FJ, Auestad A: Geriatric emergency clinical pharmacology. Emerg Med Clin North Am 1990;8:221–239.

may not be elevated even when the GFR is significantly impaired. Frequently applied formulas for creatinine clearance are fairly predictive of renal function when renal function is stable. However, age-related declines in GFR are not universal, and data from longitudinal studies suggest that as many as one-third of the elderly do not experience this age-related decline.

Liver mass decreases with an associated decrease in hepatic blood flow, which results in decreased efficiency of drug removal by hepatic extraction. Hepatic conjugation does not decline significantly with age. Xenobiotics metabolized by hepatic oxidative enzymes are eliminated more slowly with age, but decreased renal elimination of active metabolites may be the most important factor. Unlike conjugated metabolites, which tend to be inactive, products of oxidative metabolism are often active.

Lean muscle mass and total body water decline and the fat-to-lean ratio increases with advancing age. Thus, highly lipid-soluble drugs tend to have an increased volume of distribution (Vd). As a result, there may be a delay before steady state is reached, and peak effect and toxicity may occur later than expected. In contrast, drugs that distribute in water, such as ethanol, have a smaller Vd. Protein reserve diminishes with age as a result of decreased muscle mass and decreased protein synthesis. A decline in serum protein increases the free or active fraction of drugs that are otherwise highly protein bound.

PHARMACODYNAMICS

Pharmacodynamic factors may also affect a patient's response to a particular drug. In general, age-related physiologic changes in target or nontarget organs lead to increased sensitivity to a given drug, although sensitivity to some drugs also may be decreased. For example, there is evidence that β-adrenergic receptor sensitivity declines with aging, leading to a diminished response to both β-adrenergic agonists and antagonists. However, clinical experience demonstrates that the elderly respond normally to drugs of this category in terms of therapeutic response, adverse effects, and toxicity. Table 32–3 gives examples of pathophysiologic changes that frequently occur among the elderly and are unmasked by medications.

ADVERSE DRUG EVENTS

The likelihood of experiencing an ADE increases with the increasing number of drugs prescribed for a patient. Geriatric patients take more prescription and nonprescription drugs than any patient group. A complicated drug regimen reduces adherence, increases medication errors, and increases the risk of clinically important drug interactions. ADEs may occur as a consequence of drug–drug interactions but the relationship between the two phenomena is sometimes difficult to quantitate. Concurrent disease in target or nontarget organs may also alter the patient's sensitivity to a drug, resulting in a serious ADE even when the patient is given a standard or previously used dose of the drug.

Another contributing factor is physician lack of knowledge about principles of geriatric therapeutics. Compounding this is the fact that new drugs are often inadequately studied in the elderly (see Chap. 133 for further details).

Morbidity and mortality occurring in elderly patients as a result of specific drugs might be avoided if the responsible drugs were studied under the predictably high-risk conditions typically present in the elderly. If pharmacokinetic studies identify vulnerable subgroups, safe maximum doses could be recommended for specific populations at risk, theoretically limiting the risk

TABLE 32–3. Pathophysiologic Disorders Exacerbated by Drugs in the Elderly

Disorder	Drug	Possible Outcome
ADH secretion (increased)	Antipsychotics, SSRIs	Hyponatremia
Androgenic hormones (males, decreased)	Digoxin, spironolactone	Gynecomastia
Baroreceptor dysfunction, venous insufficiency	Antipsychotics, diuretics, tricyclic antidepressants	Orthostatic hypotension
Bladder dysfunction	Diuretics	Incontinence
Cardiac disease	Thiazolidinediones	Congestive heart failure
Dementia	Sedatives, anticholinergics, and many others	Confusion
Gastritis (atrophic)	NSAIDs, salicylates	Gastric hemorrhage
Immobility, cathartic bowel	Anticholinergics, opioids	Constipation
Nodal disease (sinus or AV)	β-Adrenergic antagonists, digoxin, diltiazem, verapamil	Bradycardia
Parkinson disease	Antipsychotics, metoclopramide	Parkinsonism
Prostatic hyperplasia	Anticholinergics, tricyclic antidepressants, disopyramide	Urinary retention
Thermoregulation, disordered	Antipsychotics	Hypo- or hyperthermia
Venous insufficiency	Calcium channel blockers, others	Edema

for these individuals. As a result of adverse drug events, the Food and Drug Administration (FDA) now requires sponsors of new drug applications to present effectiveness and safety data for important demographic subgroups, including the elderly, in their FDA submission data.

The use of nonprescription and herbal pharmaceuticals may cause serious adverse effects. Outdated and discontinued drugs are an additional problem for the elderly who often retain products in their homes for decades. Patients may be unwilling to change, or successive physicians might continue to renew the prescription without sufficiently reevaluating the patient.

MANAGEMENT

Management decisions must be made with the foregoing principles in mind. Gastrointestinal decontamination should proceed as in younger patients. Because constipation is a more frequent problem in the elderly, when multiple-dose activated charcoal is indicated, particular attention must be paid to gastrointestinal function and motility. The presence of clinical or subclinical heart failure or renal failure may increase the risk of fluid overload when sodium bicarbonate is used. In the elderly, hemodialysis or hemoperfusion may be indicated earlier in cases of lithium or theophylline poisoning, where elimination may be hampered by a decreased creatinine clearance or reduced endogenous clearance, respectively.

Strategies to limit unintentional toxic exposures in elderly patients with cognitive or sensory impairment should be similar to those employed in

young children, who are at high risk for ingesting toxic substances or pharmaceuticals prescribed for others in the household. The strategies should include the removal of potentially dangerous substances and unnecessary drugs from the elderly patient's environment. The physician should request that the patient or caregiver bring all medications to the office in the original bottles and then limit the number of pills dispensed. It may be necessary to limit medications such as antidepressants to a 1-week supply or to choose alternative medications with safer therapeutic toxic index ratios. Administration and control of the medications with directly observed therapy may of necessity become the responsibility of the caregiver rather than the patient.

ADMISSION CRITERIA

When geriatric patients are evaluated in the emergency department for poisonings or serious ADEs, the need for hospital admission should be guided by concerns about the patient's frailty weighed carefully against the known hazards of hospitalization for the elderly. The physician should be particularly alert to certain situations that might mandate admission: elder abuse or neglect, unresolved mental status changes, inadequate home care manifested by unexplained falls, or overdose of medications with prolonged durations of action.

Unresolved mental status changes may require close observation and hospitalization. Elderly patients who are confused or unable to walk are sometimes mistakenly assumed to be chronically impaired. Functional deterioration should not be assumed to be age related. Many very elderly patients are cognitively normal, physically robust, and independent in all activities of daily living.

Overdose with long-acting medications requires careful monitoring. Because duration of action of certain drugs may be markedly prolonged among geriatric patients, a higher degree of vigilance is required.

33 Postmortem Toxicology

Postmortem toxicology is the study of the presence, distribution, and quantification of a xenobiotic after death. This information is used to account for physiologic effects of a xenobiotic at the time of death through its quantification and distribution in the body at the time of autopsy. Several variables may cause changes in xenobiotic concentrations during the interval between the time of death and subsequent autopsy. Toxicologists and forensic pathologists may be asked to interpret postmortem xenobiotic concentrations and decide whether these substances were incidental or contributory to the cause of death.

HISTORY AND ROLE OF MEDICAL EXAMINERS

The relationship between antemortem xenobiotic exposures and death has been investigated for centuries. Currently in the United States, legal jurisdiction of death investigations is the responsibility of either coroners or medical examiners, depending on the state and/or county, with 19 states using medical examiner systems almost exclusively.

The medicolegal autopsy is performed by a forensic pathologist who attempts to establish cause and manner of death. "Cause of death" is the physiologic agent or event necessary for death to occur. For example, the presence of cyanide in the toxicologic evaluation might be sufficient to establish cardiorespiratory arrest from cyanide poisoning. "Manner of death" is an explanation of how the death occurred and broadly distinguishes natural from nonnatural (or violent) deaths. Nonnatural deaths, depending on the jurisdiction, can be divided into several categories. With the identification of cyanide, the manner of death cannot be considered natural because an intoxication is a "chemically traumatic" (violent) event. The medical examiner must make the best determination of the manner of death based on the available evidence. An unintentional exposure may be classified as an "accident" (a legal term for some unintentional nonnatural deaths), and intentional self-exposure may be classified as a "suicide." If the circumstances indicate an exposure because of the acts of another person, the manner of death is classified as a "homicide."

Determination of manner of death has important consequences. Homicide necessitates involvement of law enforcement officials for further investigation. Cases deemed suicide not only impact survivors psychologically but also may nullify life insurance payments, whereas a case deemed an accident may have a double-indemnity insurance clause. Liability suits in workplace disasters may be similarly affected if illicit drugs are identified in the postmortem specimens of involved workers.

THE TOXICOLOGIC INVESTIGATION

Ordinarily, toxicologic samples are collected as part of a complete autopsy. In a medicolegal investigation, the forensic pathologist determines the need for complete autopsy and may take jurisdiction without familial consent. Occasionally, only fluid samples are obtained if a complete autopsy is either unnecessary or the family has legal grounds for objection. The precise list of xenobiotics screened in postmortem samples varies greatly by the jurisdiction.

DECOMPOSITION AND POSTMORTEM BIOCHEMICAL CHANGES

The first stage of decomposition is autolysis where endogenous enzymes are released and normal mechanisms maintaining cellular integrity fail. Chemicals move across leaky cellular membranes down relative concentration gradients. Glycolysis continues in red blood cells until intracellular glucose is depleted, and then lactate is produced. Ultimately, intracellular ions and proteins are released into the blood, and tissue and blood acidemia develops.

The next stage of decomposition is putrefaction. This involves digestion of tissue by bacterial organisms, which typically originate in the bowel or respiratory system. If death occurs in a very warm, dry climate, such as a desert or comparably arid environment, the body may proceed to desiccate so rapidly that putrefactive changes may not occur, resulting in mummification. If the environment is very cold and hypoxic, such as at great depths under water, putrefaction will be slowed. Anoxic decomposition of fatty tissues occurs, forming a white cheesy material known as adipocere. Anthropophagia occurs in unprotected postmortem environments where insects or other animals feed on the remains.

Another process that will alter natural decompositional changes is embalming, a technique that chemically preserves tissues and can be performed in a variety of ways. Typically, blood is drained through large-vessel pumps, and an embalming fluid is injected intravascularly to perfuse and preserve the face and/or other tissues. Intracavitary spaces may be injected with the preserving substances, and solid organs may or may not be removed.

SAMPLES USED FOR TOXICOLOGIC ANALYSIS

Unless the medical examiner has suspicions about a death, only standard autopsy samples will be available in an otherwise intact body. These typically include samples of blood, gastric contents, bile, urine, and, occasionally, solid organs, such as the liver or brain. Less commonly, vitreous humor is obtained for analysis. If the decedent was hospitalized prior to death, antemortem specimens may be available for evaluation.

Blood

Postmortem cell lysis prevents the reporting of plasma concentrations, and "blood" concentrations are reported instead. Intravascular blood from the subclavian or femoral vessels is a common source for toxicologic examination.

Vitreous Humor

Because of the relatively avascular and acellular nature of the fluid, the vitreous humor is well protected from the early decompositional changes that typically occur in blood.

Urine

Urine may be available at autopsy and can reveal renally eliminated substances or their metabolites. Because the bladder serves as a reservoir in which metabolism is unlikely to occur, xenobiotics and their concentrations obtained at autopsy reflect antemortem urine concentrations.

Gastric Contents

The contents of the stomach are grossly inspected for color, odor, and for presence or absence of pill fragments, food particles, activated charcoal, or other foreign materials.

Solid Organs and Other Sources

Xenobiotic concentrations may be measured in solid organs, such as liver or brain, or in other tissues, such as hair, nails, muscle, pleural fluid, or intracranial blood.

ENTOMOTOXICOLOGY

Fluids and possibly insect parts can be analyzed in putrefied bodies or those subject to anthropophagy. Forensic entomologists take samples of these insects and can then extrapolate, by stage of insect life, environmental conditions, and season, the approximate time of death. The species *Calliphoridae*, or bluebottle fly, is attracted to unprotected remains by a very fine scent that develops within hours of death. Larvae, which feed on the decomposing tissue, can be examined for the presence of toxins.

INTERPRETATION OF POSTMORTEM TOXICOLOGIC RESULTS

Once fluid and tissue samples are collected and analyzed for the presence of xenobiotics, the process of interpreting the results begins. This complex task attempts to account for the clinical effects of a xenobiotic at the time of death by integrating medical history, autopsy findings, and toxicological reports. Multiple confounding variables can affect the sample concentrations of xenobiotics from the time of death to that of the autopsy. These can be considered as relating to the xenobiotic, the state of health of the decedent, and autopsy techniques and findings (Table 33–1).

Variables Relating to the Xenobiotic

Postmortem Redistribution

Xenobiotic blood concentration may be higher at autopsy than at the time of death if the agent undergoes significant postmortem redistribution. This redistribution occurs most often for xenobiotics with large volumes of distribution, where decomposition results in release of intracellular xenobiotic into the extracellular compartment.

Postmortem Metabolism

Less commonly, xenobiotic concentration may fall secondary to postmortem metabolism.

State of Absorption and Distribution

As in the case of the living, the state of absorption, distribution, and other toxicokinetic principles affect the sampling concentration at the time of death. In the case of a xenobiotic with minimal postmortem metabolism or redistribution, the phase of absorption is suggested by the relative quantity of the xenobiotic in different fluids and solid organs.

TABLE 33–1. Considerations in Interpreting Postmortem Xenobiotic Concentrations

Xenobiotic dependent
Pharmacokinetic considerations
State of absorption/distribution at time of death
Postmortem redistribution
Postmortem metabolism
Pharmacodynamic considerations
Expected clinical effects
Synergistic interactions
Postmortem xenobiotic stability during
Putrefaction
Preservation
Decedent dependent
Comorbid conditions
Tolerance
Pharmacogenetic variability
Autopsy dependent
Postmortem interval: state of preservation/decomposition
Previously undiagnosed conditions
Specimens sampled
Sample sites
Handling and preservation
Other
Laboratory techniques
Evidence at scene
Previously published tissue concentrations

Xenobiotic Stability

Xenobiotic stability refers to the ability to maintain molecular integrity despite changes during decomposition, storage conditions, or the addition of preservatives.

Xenobiotic Chemical Interactions

An artifact may result from a chemical interaction with a xenobiotic added during the postmortem period, such as embalming fluid.

Expected Clinical Effects of the Xenobiotic

For a fatality to be attributed to a xenobiotic, the expected clinical course of the exposure should be consistent with the autopsy findings. Interpretation of postmortem toxicology must also incorporate clinically relevant pharmacokinetic and pharmacodynamic consequences of xenobiotic interactions (eg, ethanol and benzodiazepine).

Variables Related to the Decedent

Comorbid Conditions

A thorough medical history is important and may assist in interpreting the clinical effects of a xenobiotic exposure. Certain clinical conditions may produce substances that interfere with postmortem laboratory assays.

Tolerance

Tolerance is an acquired condition in which higher and higher xenobiotic concentrations are required to produce a given clinical effect. It is an important consideration for deaths in the presence of opioids, ethanol, and sedative-hypnotics.

Pharmacogenetics

There is genetic variability in the expression of certain metabolic enzymes that affect an individual response to a xenobiotic.

Variables Relating to the Autopsy

State of Decomposition

In decedents with advanced stages of decomposition, xenobiotics can diffuse from depot compartments, such as the stomach or bladder, into adjacent tissues and blood vessels, affecting their sample concentrations.

Handling of the Body

Inappropriate handling of the body can result in artifacts. Preservatives containing metals are currently prohibited from use in embalming because they can contaminate the evaluation for metal poisoning.

Autopsy Findings

In many xenobiotic-related deaths the anatomic findings are nonspecific. In some cases, the autopsy reveals confirmatory or supportive findings, such as a large quantity of undigested pills in the stomach.

Artifacts Related to Sampling Sites

Site-specific differences in postmortem xenobiotic blood concentrations are common. Blood drawn from femoral vessels may have a low glucose concentration because of postmortem glycolysis, but the glucose concentration of blood removed from the right heart chambers may be high as a result of release of liver glycogen stores. The individual interpreting the toxicologic report must know the exact site sampled; ideally more than one site should be available for comparison.

Other Limitations

Although formulas and ranges exist for assessing xenobiotic doses or concentrations in the living, these are not necessarily applicable when analyzing postmortem samples. Although there are generalized standards of practice in forensic investigations, specimen collection and laboratory methodology may vary.

Special Considerations: Organ Procurement from Poisoned Patients

Xenobiotics can cause brain death because of the vulnerabilities of the CNS. With supportive care, however, such patients may be suitable candidates for organ donation. Early identification of donors is critical as the viability of transplantable tissue diminishes as duration of brain death progresses. Timely identification may be further complicated by the presence of xenobiotics that mimic brain death (Table SC–1).

Once brain death is established (Table SC–2), organ procurement personnel assist in obtaining familial consent, deciding which organs are most suit-

TABLE SC–1. Conditions That Can Mimic Brain Death

Guillain-Barré syndrome	Sedative-hypnotics *(cont'd)*
Hypoglycemia	Benzodiazepines
Hypothermia	Meprobamate
Poisonings	Chloral hydrate
Amitriptyline	Trichloroethylene
Bismuth salts	Pontine hemorrhage
Inhaled anesthetics	Rabies
Sedative-hypnotics	Tetrodotoxin
Barbiturates	

TABLE SC–2. Clinical Criteria for the Diagnosis of Brain Death

No alternative cause for the clinical condition (eg, hypothermia)	
Poisoning not or no longer a consideration as the cause of the clinical condition	
Coma: No motor responses to appropriate painful stimuli	
Absence of brainstem reflexes	
Pupillary responses to light and pupils at midposition (4–6 mm)	
Corneal reflexes	
Caloric (oculocephalic) responses	
Gag reflex	
Coughing in response to tracheal suctioning	
Sucking and rooting reflexes	
Apnea test	
Absence of a respiratory drive at a $PaCO_2$ that is 60 mm Hg or 20 mm Hg above normal baseline values	
Interval between 2 evaluations, according to patient's age	
Term to 2 mo, 48 h	>1 yr to <18 yr, 12 h
>2 mo to 1 yr, 24 h	≥18 yr, interval optional
Confirmatory tests	
Term to 2 mo, 2 confirmatory tests	>1 yr to <18 yr, optional
>2 mo to 1 yr, 1 confirmatory test	≥18 yr, optional
Confirmatory tests include:	
Cerebral angiography	Electroencephalography
Cerebral scintigraphy	Transcranial Doppler ultrasonography

$PaCO_2$: partial pressure of CO_2 obtained on an arterial blood gas.
Adapted from Wijdicks EF: The diagnosis of brain death. N Engl J Med 2001;344:1215–1221.

TABLE SC–3. Successful Organ Transplants after Donor Poisonings

Organ	Xenobiotics Identified
Cornea[a]	Brodifacoum, cyanide
Heart	Acetaminophen, benzodiazepines, β-adrenergic antagonists, brodifacoum, carbamazepine, carbon monoxide, clomethiazole, cyanide, digitalis, digoxin, ethanol, flurazepam, glyburide, insulin, meprobamate, methanol, organic phosphorus compounds, propoxyphene, thiocyanate
Kidney[a]	Acetaminophen, brodifacoum, carbon monoxide, cyanide, ethylene glycol, methanol, tricyclic antidepressants
Liver	Brodifacoum, carbon monoxide, cyanide, ethylene glycol, methanol, tricyclic antidepressants
Lung	Brodifacoum, carbon monoxide, methanol
Pancreas	Acetaminophen, brodifacoum, carbon monoxide, cyanide, ethylene glycol, methanol, tricyclic antidepressants
Skin	Cyanide

[a]Can be cadaveric procurement.

able for transplant, and maximizing physiologic support and perfusion until organ procurement occurs. Successful transplantation of organs from donors poisoned with a multitude of xenobiotics is reported (Table SC–3).

The 1-year survival in recipients from poisoned donors approximates that from nonpoisoned donors and was reported at 75% in one series. Additionally, in most transplant failures from poisoned donors, the causes are rejection, sepsis, or technical reasons, not the xenobiotic.

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PART C THE CLINICAL BASIS OF MEDICAL TOXICOLOGY

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Section I. Case Studies

A. Analgesics and Antiinflammatory Medications

34 | Acetaminophen

HISTORY AND EPIDEMIOLOGY

Acetaminophen (*N*-acetyl-*p*-aminophenol [APAP]) was first used clinically in the United States in 1950. Acetaminophen has since proven to be a remarkably safe drug at appropriate dosage, which has made acetaminophen the analgesic-antipyretic of choice in many circumstances. Acetaminophen is available alone in a myriad of single-agent dose formulations and delivery systems, and also in a variety of combinations with opioids, other analgesics, sedatives, decongestants, expectorants, and antihistamines.

The diversity and wide availability of acetaminophen products dictate that acetaminophen toxicity be considered not only after identified acetaminophen exposures, but also after exposure to unknown or multiple drugs in settings of drug overdose, drug abuse, and therapeutic misadventures. The Toxic Exposure Surveillance System of the American Association of Poison Control Centers reports well over 100,000 calls to US poison centers each year resulting from potential acetaminophen exposures, and there are more hospitalizations reported after acetaminophen overdose than after overdose of any other common pharmaceutical (Chap. 130).

Despite enormous experience with acetaminophen toxicity, many controversies and challenges remain unresolved. To best understand the continuing evolution in approach to acetaminophen toxicity, it is critical to start with an analysis of certain fundamental principles and then to apply these principles to both typical and atypical presentations in which acetaminophen toxicity must be considered.

PHARMACOLOGY

Acetaminophen is an analgesic and antipyretic with weak peripheral antiinflammatory properties. Analgesic activity is reported at a serum acetaminophen concentration ([APAP]) of 10 μg/mL and antipyretic activity at 4–18 μg/mL. Antipyresis is mediated by CNS inhibition of prostaglandin E_2 (PGE_2) synthesis either via direct inhibition of cyclooxygenase (COX)-2 or inhibition of membrane-associated PGE synthase. The analgesic effect of acetaminophen is also mediated by its central inhibition of COX-2 and prostaglandin synthase, as well as possible indirect modulation of serotonergic pathways.

PHARMACOKINETICS

Following oral ingestion, immediate-release acetaminophen is rapidly absorbed with a time to peak [APAP] of approximately 45 minutes. Liquid acetaminophen has a time to peak of 30 minutes. Extended-release acetamino-

phen has a time to peak of 1–2 hours but is almost entirely absorbed by 4 hours. Time to peak is delayed by food and coingestion of opioids or anticholinergics. Oral bioavailability is 60–98%. Peak [APAP] after a recommended dose ranges from 8–32 μg/mL. Acetaminophen has a total protein binding of 10–30%, which does not change in overdose. APAP crosses both the placenta and the blood–brain barrier.

First-pass metabolism removes 25% of a therapeutic dose. Once absorbed, approximately 90% of acetaminophen normally undergoes hepatic conjugation with glucuronide (40–67%) and sulfate (20–46%) to form inactive metabolites, which are eliminated in the urine. A small fraction of unchanged acetaminophen (<5%) and other minor metabolites reach the urine but are not thought to be clinically relevant. The remaining fraction, usually ranging from 5–15%, is oxidized by CYP2E1 (and to a lesser extent, CYP2A6, CYP1A2, and CYP3A4) resulting in the formation *N*-acetyl-*p*-benzoquinoneimine (NAPQI). Glutathione (GSH) quickly combines with NAPQI; the resulting complex is then converted to nontoxic cysteine or mercaptate conjugates, which are then eliminated in the urine (Fig. 34–1). The elimination half-life of acetaminophen is about 2–3 hours after a nontoxic dose but may become prolonged in patients who develop hepatotoxicity.

TOXICOKINETICS

Even after overdose, the majority of acetaminophen absorption occurs within 2 hours. Peak plasma concentrations generally occur within 4 hours, although later peaks are rarely documented in overdoses. After clinically significant overdose, saturation of the normal nontoxic routes of metabolism becomes important in the development of toxicity. The amount of NAPQI formed by CYP2E1 is increased disproportionately to the acetaminophen dose because maximal rates of sulfation and glucuronidation are exceeded (Fig. 34–1).

PATHOPHYSIOLOGY

With therapeutic acetaminophen dosing, the GSH supply far exceeds that which is required to detoxify NAPQI, and no toxicity occurs. After overdose, the rate and quantity of NAPQI formation outstrips GSH supply and regeneration, resulting in free NAPQI rapidly binding to hepatocyte constituents. Once NAPQI formation exceeds the GSH availability, it covalently binds and arylates critical cell proteins, inducing a series of events that result in cell death. This covalent binding and arylation occurs rapidly after glutathione depletion and within hours of ingestion.

Factors that may predispose patients to hepatotoxicity include increased frequency of acetaminophen dosing, prolonged duration of excessive dosing, increased capacity for CYP2E1 activation to NAPQI, decreased GSH availability, and decreased capacity for glucuronidation and sulfation. Potentially more important than the actual concentration of GSH or the activity of CYP2E1 is the balance of these two important factors. Despite experimental evidence for all of the above, clinical consideration of these factors is complex and controversial and is discussed later.

The pathophysiology of most organ dysfunction resulting from acetaminophen toxicity is a result of the local formation of acetaminophen metabolites. Renal formation of NAPQI is the likely cause of acute proximal renal tubular necrosis after acute overdose. Similarly, injury to other organs, such as the heart, pancreas, and CNS, also occur. An acetaminophen-induced

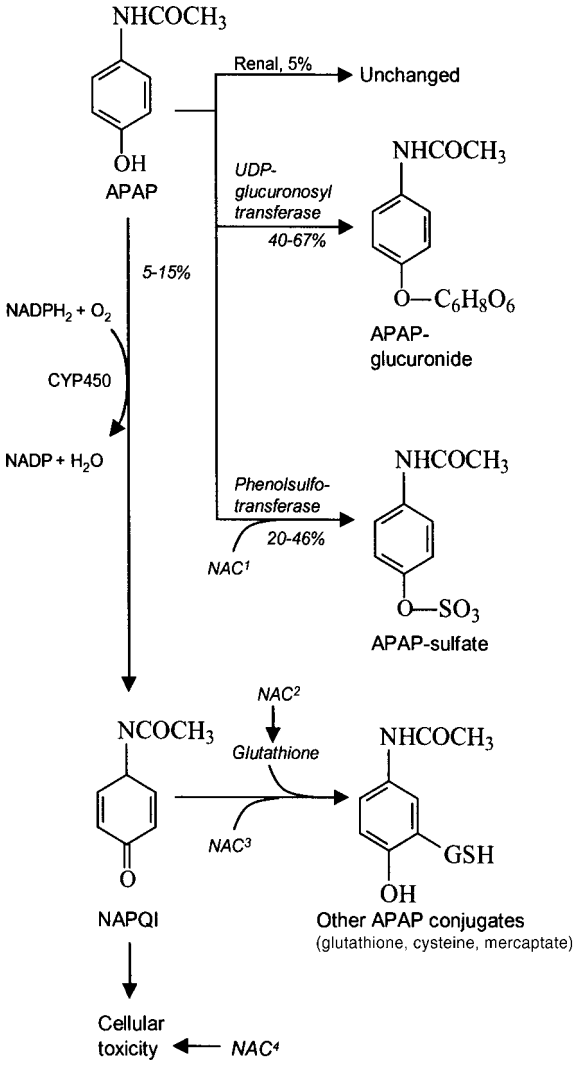

FIG. 34–1. Important routes of acetaminophen metabolism in man and mechanisms of *N*-acetylcysteine (NAC) hepatoprotection. NAC^1 augments nontoxic sulfation. NAC^2 is a glutathione (GSH) precursor. NAC^3 is a GSH substitute. NAC^4 improves multiorgan function during hepatic failure and possibly limits extent of hepatocyte injury. APAP = *N*-acetyl-*p*-aminophenol.

metabolic acidosis also may occur as an early manifestation after massive ingestion of APAP, typically in association with depression of mental status. The elevated anion gap acidosis may or may not be accompanied by hyperlactatemia.

CLINICAL MANIFESTATIONS

Early recognition and treatment of patients with acetaminophen poisoning are essential in order to minimize morbidity and mortality. This task is made difficult by the lack of predictive clinical findings early in the course of acetaminophen poisoning. Clinicians should not be reassured by the absence of clinical symptoms shortly after ingestion. The first symptoms after acetaminophen overdose may be those of hepatic injury, which develop many hours after the ingestion, when antidotal therapy will have diminished efficacy.

The clinical course of acute acetaminophen toxicity can be described in four stages.

Stage I: Hepatic injury has not yet occurred and patients are asymptomatic or have nonspecific clinical findings (eg, nausea, vomiting, malaise). Laboratory indices of liver function are normal.

Stage II: Onset of liver injury, generally within 24 hours after ingestion, but is nearly universal by 36 hours. Symptoms and signs vary with the severity of liver injury. Aspartate aminotransferase (AST) is the most sensitive, widely available measure to detect the onset of hepatotoxicity. When discussing APAP, by convention hepatotoxicity is defined as a peak AST above 1000 IU/L. Although lower peak concentrations of AST represent some injury to hepatic tissue, they rarely have any clinical relevance.

Stage III: Maximal hepatotoxicity most commonly occurs between 72 and 96 hours after ingestion. The clinical manifestations include fulminant hepatic failure with encephalopathy, coma, or exsanguinating hemorrhage. Laboratory studies are also variable: AST and alanine aminotransferase (ALT) concentrations above 10,000 IU/L are common, even in patients without other evidence of liver failure. Much more important than the degree of aminotransferase elevation, abnormalities of prothrombin time, bilirubin, glucose, lactate, phosphate, and pH indicate the degree of liver failure and are essential determinants of prognosis and treatment. Fatalities from fulminant hepatic failure generally occur between 3 and 5 days after an acute overdose. Death results from either single or combined complications of multiorgan failure, including hemorrhage, acute respiratory distress syndrome (ARDS), sepsis, and cerebral edema.

Stage IV: Recovery phase. Hepatic regeneration, which generally takes several days to a few weeks, becomes complete in survivors.

Renal function abnormalities occur in as many as 25% of patients with significant hepatotoxicity, and in more than 50% of those with hepatic failure. Serious clinical manifestations other than hepatic and renal injury are unusual.

DIAGNOSTIC TESTING

Assessing the Risk of Toxicity

Principles That Guide the Diagnostic Approach

Fatalities from acetaminophen overdose are common but preventable by timely diagnosis and treatment with *N*-acetylcysteine (NAC). At the same time, the overwhelming majority of acetaminophen exposures result in no toxicity. Consequently, an appropriate approach must avoid the enormous costs of unnecessary overtreatment while eliminating patient risk. To balance these seemingly divergent goals, the clinician must understand the basis for and sensitivity of current toxicity screening methods.

Risk Determination after Acute Overdose

Acute overdose is usually considered to be a single ingestion or may be arbitrarily defined as one in which the entire ingestion occurs within a single 4-hour period. Doses of 7.5 g in an adult or 150 mg/kg in a child are widely considered as the lowest acute dose capable of causing toxicity. The dose history should be used in the assessment of risk only if there is reliable corroboration or direct evidence of validity. When the history is unreliable (as in those attempting self-harm) or suggests possible risk, the reported dose is insufficient evidence on which to base treatment decisions, and risk should then be assessed using determination of [APAP].

Interpretation of [APAP] after acute exposures is based on adaptation of the Rumack-Matthew nomogram (Fig. 34–2). The current discriminatory line ("treatment line") stretches from an [APAP] of 150 μg/mL at 4 hours to 37.5 μg/mL at 12 hours, and ends at 4.7 μg/mL 24 hours after the overdose, which is a 4-hour half-life. However, the half-life of acetaminophen was not a factor in the development of the nomogram. Although patients who develop hepatotoxicity tend to have [APAP] half-lives greater than 4 hours, use of an [APAP]

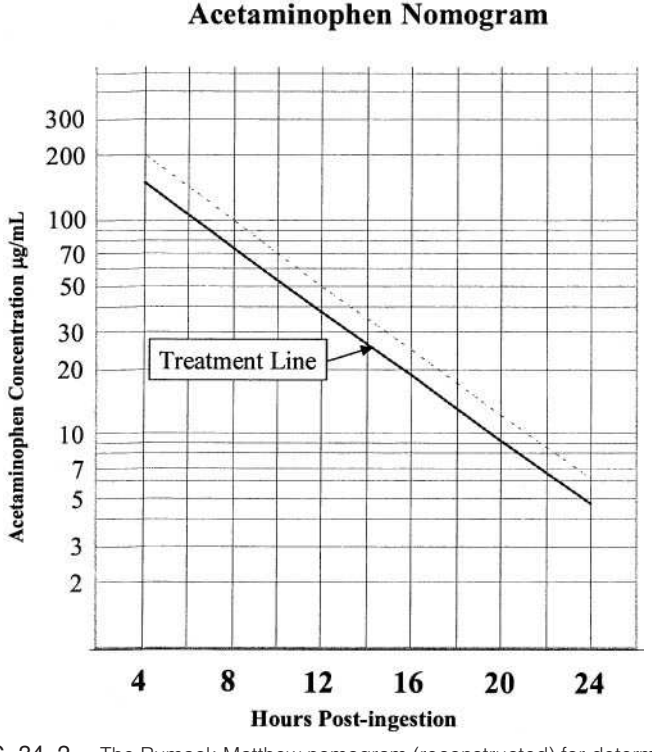

FIG. 34–2. The Rumack-Matthew nomogram (reconstructed) for determining the risk of acetaminophen-induced hepatoxicity following a single acute ingestion. Levels above the treatment line on the nomogram indicate the need for *N*-acetylcysteine therapy.

half-life to determine risk is not practical. It is important to realize that the line was based on aminotransferase elevation rather than on hepatic failure or death, and was chosen to be very sensitive, with little regard to specificity. Without antidotal therapy, only 60% of those with an initial [APAP] above this original line will develop hepatotoxicity as defined by aminotransferase values above 1000 IU/L. The incidence of nomogram failures in the United States, using this line, is only 1–3% (depending on time to treatment) and most likely results predominantly from inaccurate ingestion histories. This highlights the importance of determining the time "window" during which the acetaminophen exposure occurred, and if the time is uncertain, to use the earliest possible time as the time of ingestion.

The goal should be to determine [APAP] at the earliest point at which it will be meaningful in decision making. Measurement of [APAP] at least 4 hours after ingestion or as soon as possible thereafter is used to *confirm* risk of toxicity, and thus the need to initiate NAC. Although it is optimal to start NAC therapy as soon as possible after confirmation of risk, most patients will have excellent outcomes if therapy is started earlier than 8 hours after the overdose. Although this fact is not a license to delay the initiation of NAC until 8 hours after ingestion, it allows clinicians some leeway to wait for the laboratory to return the results of the [APAP] prior to starting therapy in patients where the history of ingestion suggests that the concentration will fall below the treatment line.

Determination of Risk When the Acetaminophen Nomogram Is Not Applicable

Risk Determined When Time of Ingestion Is Unknown

It is almost always possible to at least establish a time window during which the exposure must have occurred and then use the earliest possible time of exposure as the time of ingestion for risk-determination purposes. If this time window cannot be established or is so broad that it encompasses a span of more than 24 hours, the following approach is suggested. Determine both the [APAP] and the AST. If the AST is elevated, regardless of [APAP], treat with NAC. If the [APAP] is below the lower level of detection and the AST is normal, there is no evidence that subsequent consequential hepatic injury is possible, and NAC is unnecessary. In the remaining cases, in which the time of ingestion is completely unknown and [APAP] is detectable, it is prudent to assume that the patient is at risk and initiate treatment with NAC.

Risk Assessment after Extended-Release Acetaminophen

Unless unusual circumstances are evident, a single [APAP] determination, plotted on the nomogram, should be adequate to exclude the need for antidotal therapy, even after extended-release acetaminophen overdose. However, the validity of this conclusion requires ongoing evaluation, and any new type of alternative-release acetaminophen formulations need to be evaluated individually.

Patients with Signs or Symptoms of Hepatic Injury after Acute Ingestion

Patients who present with signs or symptoms of hepatic injury after acute acetaminophen ingestion should be immediately started on NAC and have AST and [APAP] measured. In those patients with an elevated AST and an [APAP] that is below the treatment line, the history should be reviewed with respect to the timing of the ingestion and repeat excessive acetaminophen

dosing. NAC therapy should continue while the patients are thoroughly evaluated for causes of hepatic failure, as well as other causes of elevated AST.

Risk Determination after Chronic Overdose Exposure

There are no well-established guidelines for risk determination after repeated acetaminophen exposures; nonetheless, careful interpretation of laboratory testing may make a relative risk assessment possible. Although it is possible that certain patients may be at high risk for hepatotoxicity (eg, alcohol abusers, the malnourished, those on CYP2E1 inducers), this is conceptual and not proved. In general, the incidence of serious acetaminophen toxicity after repeated doses is negligible and appears to only follow massive dosing or prolonged excessive dosing. The chronic ingestion of "maximal therapeutic" doses (4 g/d) in normal adults generally appears to be safe, even in alcohol abusers. Thus far, no upper limit for safe repeated dosing has been established.

When there is concern about toxicity risk after repeated excessive acetaminophen dosing, a logical screening laboratory evaluation consists of determination of [APAP] and AST, with additional testing as indicated by these results and other clinical features. The objective is to identify the 2 conditions that would warrant NAC therapy: remaining acetaminophen yet to be metabolized or potential serious liver injury.

Role of History and Physical Examination in Chronic Overdose

The first consideration when evaluating a patient with a history of repeated excessive acetaminophen dosing is the presence or absence of signs or symptoms of hepatotoxicity. Regardless of risk factors or dosing history, such findings should prompt treatment with NAC and laboratory evaluation. This is particularly important since most reported cases of serious toxicity after repeated dosing are symptomatic for more than 24 hours prior to diagnosis, and earlier diagnosis should improve outcome. In the asymptomatic patient, the next consideration should be the presence or absence of factors that potentially predispose the patient to toxicity. If no "high-risk" (i.e., liver disease, CYP induction, chronic alcoholism) factors are present, then asymptomatic adults who ingest 7.5 g or more in a 24-hour period should have a laboratory evaluation. It is reasonable to use a history of a daily dose of >4 g in adults or >90 mg/kg in children as a conservative cutoff for considering laboratory evaluation of asymptomatic patients who are at *high risk*.

Role of Laboratory Evaluation in Chronic Overdose

Patients with elevated AST values are considered at risk, regardless of [APAP]. The [APAP] is useful in patients with normal AST values as a tool to determine only whether there is sufficient remaining acetaminophen to lead to subsequent NAPQI formation and delayed hepatotoxicity. In some cases, the AST will be normal and the [APAP] will be <10 μg/mL, obviating the need for NAC. If the AST is normal, patients should be considered at risk if the [APAP] is higher than expected. Additional laboratory evaluation should include tests to assess hepatotoxicity, as well as prognosis (creatinine, prothrombin time, lactate, pH, and phosphate).

Determination of Risk Subgroups after Chronic Acetaminophen Exposure

Using a strategy that describes risk in a relative manner, we consider patients to be at *higher risk* in these situations: the AST is greater than twice

normal, even if the patient is asymptomatic; the AST is elevated and the patient is either symptomatic or the [APAP] >10 μg/mL; or the [APAP] is greater than expected. In these cases, treatment with NAC is recommended. Patients who are asymptomatic have less-than-expected [APAP] and a normal AST, or who have an [APAP] <10 μg/mL and an AST that is less than twice normal, are considered *low risk*. Followup by telephone or by return visit in 24 hours is recommended for *low-risk* patients and they should be given discharge instructions to return immediately for any symptoms of hepatic injury such as nausea, vomiting, abdominal pain, or constitutional symptoms. Those patients with a normal AST and an [APAP] <10 μg/mL represent *minimal risk,* and NAC is not recommended. *Minimal-risk* patients should be instructed to return immediately if symptoms of hepatic injury arise. The theoretical patient with impending toxicity but without signs or symptoms of toxicity, who might be missed by the above approach, can still be detected in a timely manner by appropriate patient discharge instruction and followup.

Risk Determination after Acetaminophen Exposure in Children

Serious hepatotoxicity after acute overdose is less common in children than in adults, but it is unclear whether this difference reflects relative hepatoprotection or merely results from differences in the characteristics of poisoning in children. Serious hepatotoxicity or death after acute acetaminophen overdose is extremely rare in children. Although limited by methodology, recent studies advocate increasing the threshold acetaminophen dose requiring screening tests after pediatric acute overdose. We advocate continued use of 150 mg/kg as the risk-defining dose and use of the treatment line for [APAP] screening until valid data demonstrate that children are selectively protected, or until accumulated experience with a higher dose threshold for screening proves safe. Following excessive repeated acetaminophen dosing, there is no evidence that children are relatively protected.

Risk Determination after Acetaminophen Exposure in Pregnancy

The initial risk of toxicity of a pregnant patient is similar to that of a nonpregnant patient, with a few exceptions. There is little evidence to suggest that any alteration of the treatment line is necessary. There is every indication that NAC is both safe and effective to treat the mother, but there are inadequate data to evaluate efficacy in the fetus, although fetal outcome has generally been excellent after maternal treatment with NAC.

Ethanol and Risk Determination

There is no evidence that chronic ethanol use should alter the approach after an APAP acute overdose. Because of the potential failure of the higher original nomogram to adequately screen alcoholics and those chronically taking P450 inducers, some authors suggest that a much lower standard should be used. The treatment line is adequately sensitive for screening after an acute APAP overdose, regardless of the patient's pattern of ethanol use. The relationship between chronic ethanol use and chronic APAP use is complex and these patients should be managed similarly to those with chronic overdose.

Assessing Actual Toxicity: Critical Components of the Diagnostic Approach

Initial Testing

As outlined above, in patients with acute acetaminophen overdose and no evident hepatotoxicity, [APAP] should be measured, but no other initial laboratory assessment is required. Patients considered to be at risk for APAP toxicity according to the nomogram or by history (in the case of repeated excessive dosing), or in those suspected of already having mild hepatotoxicity by history and physical examination, should also have AST measured.

Ongoing Monitoring and Testing

If no initial AST elevation is noted, repeated AST determination alone—without other biochemical testing—every 24 hours until completion of treatment, is sufficient to exclude the development of hepatotoxicity. If AST elevation is noted, then the prothrombin time and creatinine should be measured and repeated every 24 hours, or more frequently if clinically indicated. If evidence of actual liver failure is noted, then careful monitoring of blood glucose, creatinine, phosphate, lactate, and acid–base status are important in assessing extrahepatic organ toxicity and are vital in assessing the function of the liver and the patient's potential need for transplant (see assessing prognosis below).

MANAGEMENT

Limiting Gastrointestinal Absorption

In general, gastric emptying is not a consideration for patients with isolated acetaminophen overdose because of the very rapid gastrointestinal absorption of acetaminophen and the availability of an effective antidote. However, the early administration of activated charcoal shortly after APAP ingestion appears to decrease the number of patients who have [APAP] above the treatment line.

Antidotal Therapy with NAC

Mechanism of Action of NAC

NAC *prevents* toxicity by limiting the formation of NAPQI, increases the capacity to detoxify NAPQI that is formed, and *treats* hepatotoxicity through nonspecific mechanisms. NAC prevents toxicity by serving as a glutathione precursor, leading to increased GSH availability. NAC can also serve as a GSH substitute, combining with NAPQI and being converted to cysteine and mercaptate conjugates, just as GSH is converted. Based on large clinical trials, it appears that NAC efficacy is nearly complete as long as it is initiated within 8 hours of an acute overdose (see Fig. 34–1).

Intravenous versus Oral Administration

As with many issues related to acetaminophen toxicity, the choice of oral versus intravenous NAC is complex. Available information suggests that there are advantages and disadvantages to each, and settings in which each may be more appropriate than the other. Because there have been no controlled head-to-head studies comparing IV and oral NAC, conclusions about the relative benefits of each is largely speculative.

With the exception of established liver failure, where only the intravenous route has been investigated, intravenous and oral NAC administration are equally efficacious in treating acetaminophen toxicity.

Safety is the best understood of these issues; oral NAC clearly has fewer severe side effects than IV NAC. Intravenous NAC is associated with a 17% rate of anaphylactoid reactions, of which 1% are severe. These anaphylactoid reactions are typically minor and include rash, flushing, vomiting, and bronchospasm, but in rare instances, may lead to hypotension and death. Even when urticaria, angioedema, and respiratory symptoms develop, they are usually easily treated and NAC can be subsequently restarted with a very low incidence of recurrence. Although proper dosing of IV NAC is very safe, it must nevertheless be considered more dangerous than oral NAC because of the risk of dosing errors. An additional safety concern with the use of intravenous NAC is the potential problem associated with the improper concomitant infusion of large volumes of free water to children, which in some instances, leads to hyponatremia and seizures.

Duration of NAC Treatment

Results from the use of the traditional 20-hour IV NAC protocol, 48-hour and 36-hour IV NAC protocols studied in the United States, one oral 20-hour protocol, and other "short-course" dosing protocols indicate that all therapies are safe and effective in patients who are treated within 8 hours of an acute ingestion. Regardless of the protocol initiated (IV 20-hour, PO 72-hour, IV 48-hour, IV 36-hour), [APAP] and AST should be measured at the completion of the course, and NAC therapy should be continued beyond the prescribed protocol time if there is evidence of significant liver injury (AST greater than normal) or acetaminophen metabolism is incomplete ([APAP] >10 μg/mL).

Both the oral NAC data and the liver failure study seem to confirm the importance of longer duration of NAC when treating already established liver injury. The IV NAC dosing protocol that has proven beneficial in liver failure is the same initial dosing as the 20-hour IV protocol (see Antidotes in Brief, *N*-acetylcysteine), but with the IV infusion continued until the resolution of liver failure. These observations suggest that, rather than a single duration of therapy for all patients, it is appropriate to extend treatment protocols based on the clinical course of the patient.

Assessing Prognosis

The availability and success of liver transplantation after acetaminophen-induced liver failure creates an important need for early prognostic assessment. One strategy for prognostication uses a combination of clinical features of fulminant hepatic failure and is called the King's College Hospital criteria. The single criterion of pH <7.30 after fluid and hemodynamic resuscitation, or the combination of a prothrombin time (PT) >100 seconds, creatinine >3.3 mg/dL, and grade III or IV encephalopathy, is predictive of a patient who will die without transplant. Any patient meeting or approaching these criteria should be considered for transplant and is best managed in a transplant center.

A blood lactate concentration >3.5 mmol/L at a median time of 55 hours after APAP ingestion or blood lactate >3.0 mmol/L after fluid resuscitation is both a sensitive and specific predictor of patient death without transplant. An Acute Physiology and Chronic Health Evaluation (APACHE) II score >15 in isolated APAP ingestions may be as specific as the above criteria, and slightly more sensitive. A serum phosphate >1.2 mmol/L (3.75 mg/dL) on day 2 (48–72 hours) is also both sensitive and specific for predicting patients who either received a transplant or died from APAP hepatotoxicity.

N-Acetylcysteine

N-Acetylcysteine (NAC) is the cornerstone of therapy for patients with potentially lethal acetaminophen (*N*-acetyl-*p*-aminophenol; APAP) overdose. NAC also has a role in limiting toxicity caused by glutathione depletion and free radical formation, such as from carbon tetrachloride, chloroform, pennyroyal oil, and possibly valproic acid.

Finally, NAC is useful in the management of fulminant hepatic failure caused by toxicologic and nontoxicologic etiologies. Its beneficial effects are also under investigation in critically ill patients with a variety of stress-induced disorders, perhaps in the prevention of further renal impairment in patients with chronic renal insufficiency administered a radiographic-contrast agent, although this was recently challenged, and in those with hepatorenal syndrome. Furthermore, following exposure to certain metals such as cobalt and chromium, NAC is potentially beneficial.

HISTORY

Early experiments demonstrated that NAC could prevent acetaminophen-induced toxicity in mice when treatment was initiated within 4.5 hours of ingestion and that the oral and intravenous (IV) routes were equally efficacious when treatment was initiated within 1 hour of ingestion. The US Food and Drug Administration approved oral NAC in 1985 and IV NAC in 2004.

MECHANISM OF ACTION

When administered shortly following acetaminophen ingestion, NAC prevents toxicity largely by acting as a glutathione precursor. Later in the clinical course, after *N*-acetyl-*p*-benzoquinoneimine (NAPQI) has covalently bound to hepatocellular protein, NAC modifies the subsequent toxin-induced inflammatory response.

NAC may act directly as an antioxidant; act as a reservoir for thiol groups; increase nitric oxide synthase to improve blood flow by combining with nitric oxide to form the potent vasodilator *s*-nitrosothiol; and increase formation of essential endogenous antioxidants such as glutathione. In this manner, NAC can modulate the oxidative stress and inflammatory cascade while improving oxygen delivery and extraction in extrahepatic organs such as the brain and heart and kidney.

CLINICAL USE

If the patient's history suggests an acute acetaminophen ingestion of ≥150 mg/kg in children or 7.5 g in adults and the results of blood tests will not be available within 8 hours of the ingestion, or if serum [APAP] concentration falls on or above the treatment line on the Rumack-Matthew nomogram, NAC should also be instituted expeditiously. NAC should also be administered to most patients with chronic overdose while awaiting the aspartate

aminotransferase (AST) and [APAP], and when hepatotoxicity is manifest by symptoms or liver enzyme elevations (Chap. 34).

PHARMACOKINETICS

When NAC is administered, it is present in plasma in the reduced or oxidized state and is either free or bound with other thiols such as *N*-acetylcysteine-cysteine. NAC is metabolized to many sulfur-containing compounds such as cysteine, glutathione, methionine, cystine, disulfides, and conjugates.

Conflicting data regarding the concomitant use of activated charcoal suggest that the resultant bioavailability of NAC is either decreased or unchanged. This interaction is of limited importance now that IV *N*-acetylcysteine is available. Oral absorption of NAC is rapid, with a mean time to maximum peak concentration of 1.4 ± 0.7 hours, but the bioavailability is low (10–30%) because of significant first-pass metabolism. NAC has a relatively small volume of distribution (0.5 L/kg), and protein binding is 83%. Serum concentrations after IV administration of an initial loading dose (150 mg/kg over 15 minutes) reach about 500 mg/L. A steady-state plasma concentration of 35 mg/L (10–90 mg/L) is reached in about 12 hours with the standard IV protocol. Its elimination half-life is 5.7 hours. Severe liver damage does not appear to affect NAC elimination.

ORAL *N*-ACETYLCYSTEINE VERSUS INTRAVENOUS *N*-ACETYLCYSTEINE

Although there has never been a direct comparison between these approaches, they appear to confer equal protection when either is administered within 8 hours. The 21-hour intravenous NAC protocol is 150 mg/kg loading dose over 60 minutes, followed by an additional dose of 50 mg/kg over 4 hours, and then 100 mg/kg over 16 hours, for a total dose 300 mg/kg. The 72-hour oral regimen is a 140-mg/kg loading dose followed by 70 mg/kg for 17 additional doses, for a total dose of 1330 mg/kg. Both protocols are effective in preventing hepatic damage when given within 8 hours of acetaminophen ingestion. The 72-hour oral NAC regimen appears superior to the 20-hour IV NAC protocol when begun at 16–24 hours postingestion, most likely due to the increased duration of the regimen (see addendum at end of chapter).

We now recommend IV NAC for essentially all patients without asthma or bronchospasm and no history of a prior anaphylactoid reaction or contraindication to IV NAC, and in patients in whom the development of an anaphylactoid reaction can be tolerated. Oral NAC should be considered when it is unlikely that the full course of therapy is indicated.

The appropriate dilution of IV NAC in children is problematic. A 2% final NAC concentration in 5% dextrose in water (D_5W) is suggested to avoid local effects of the recommended hyperosmolar solution. Hyponatremia is possible and sodium concentrations and fluid requirements should be meticulously monitored. For these reasons oral NAC may be preferred in small children.

USE IN PREGNANCY AND NEONATES

NAC is FDA Pregnancy Category B. Untreated acetaminophen toxicity is a far greater threat to the fetus than NAC treatment. Human data demonstrate that NAC traverses the placenta and produces cord blood concentrations comparable to maternal blood concentrations. No adverse effects were observed when preterm newborns were treated with IV NAC.

USES OTHER THAN ACETAMINOPHEN

Diverse investigations of NAC as a treatment for a number of xenobiotics associated with free radical or reactive metabolite toxicity are reported. Some of these xenobiotics include chloroform, carbon tetrachloride, 1,2-dichloropropane, acrylonitrile, doxorubicin, cyclophosphamide, and pennyroyal oil.

ADVERSE EFFECTS AND SAFETY ISSUES

Oral NAC may cause nausea, vomiting, flatus, diarrhea, gastroesophageal reflux, and dysgeusia; generalized urticaria occurs rarely. Anaphylactoid reactions described after IV dosing of NAC are not noted after oral therapy and may be either rate related, concentration related, or related to high serum NAC concentrations.

The IV route assures delivery, but rate-related anaphylactoid reactions are possible. The original package insert for Acetadote (acetylcysteine) recommended infusing the loading dose over 15 minutes, but it was subsequently changed to an infusion over 1 hour to reduce the potential for life-threatening anaphylactoid reactions. The manufacturer categorizes the number of anaphylactoid reactions occurring in 109 patients receiving the 15-minute loading dose as mild, (6%), moderate (10%), and severe (1%).

If angioedema or an anaphylactoid reaction characterized by hypotension, shortness of breath or wheezing, flushing, or erythema occurs, the NAC should be stopped and standard symptomatic therapy instituted. Once the reaction resolves NAC can be carefully readministered after an hour. If the reaction persists or worsens, discontinue IV NAC and consider switching to oral NAC. Adverse reactions confined to flushing and erythema are usually transient, and NAC may be continued with meticulous monitoring. Urticaria can be managed with diphenhydramine with the same precautions. Iatrogenic overdoses with IV NAC have been fatal in small children.

DOSING

The manufacturer recommends a loading dose of 150 mg/kg in 200 mL of D_5W (for adults) infused over 60 minutes, followed by a first maintenance dose of 50 mg/kg in 500 mL of D_5W (for adults) infused over 4 hours, followed by a second maintenance dose of 100 mg/kg in 1000 mL of D_5W (for adults) infused over 16 hours. The current manufacturer's recommended dilution of NAC for small children should be followed to avoid fluid and electrolyte problems.

When NAC is administered orally, the patient should receive a 140-mg/kg loading dose either orally or by enteral tube. Starting 4 hours after the loading dose, 70 mg/kg should be given every 4 hours for an additional 17 doses. The solution should be diluted to 5% with a soft drink to enhance palatability. Antiemetics (such as metoclopramide) or a serotonin antagonist (such as ondansetron) should be used to ensure absorption, if indicated. The standard approach is to receive 72 hours of oral NAC therapy, although shorter courses may be acceptable (Chap. 34).

If hepatic failure intervenes, IV NAC should be administered at a dose of 150 mg/kg in D_5W infused over 24 hours and continued until the patient has a normal mental status (or recovers from hepatic encephalopathy), the patient's international normalized ratio (INR) becomes <2.0, or the patient receives a liver transplant. Before the FDA approval of Acetadote, NAC approved for oral administration was administered by the IV route, often while using a 0.22-μm

filter as a delivery precaution. Unless there were extenuating circumstances, we would no longer recommend this practice.

AVAILABILITY

Acetadote (NAC) is available as a 20% concentration in 30-mL single-dose vials designed for dilution prior to IV administration. NAC for oral administration is available in 10-mL vials of 10% and 20% for oral administration.

ADDENDUM

In the United States, the current recommended loading dose for IV NAC is 150 mg/kg over 60 minutes. Previously, and in much of the rest of the world, the loading dose is administered over 15 minutes. This results in a 21-hour and a 20-hour protocol, respectively. Although these two regimens are believed to be pharmacologically equivalent, both terms have been retained here for accuracy.

35 | Salicylates

EPIDEMIOLOGY

Since the year 2000, the category for analgesics has consistently ranked first among both the substances most frequently reported to poison centers in the United States and those responsible for the largest number of deaths. Of the analgesic-related deaths reported, aspirin, alone or in combination, accounts for approximately 12.6%.

PHARMACOLOGY

Aspirin and other salicylates are analgesics and antiinflammatory agents, as well as antipyretics. Most of the beneficial effects are a result of inhibition of cyclooxygenase (COX), the enzyme that enables the synthesis of prostaglandins, which, in turn, mediates inflammation and fever. Independent of their effects on prostaglandins, salicylates also directly inhibit neutrophils, which contributes to their antiinflammatory effects. The type of pain for which salicylates are purportedly most effective is the pain that accompanies inflammation and tissue injury. Such pain is elicited by prostaglandins, which are liberated by bradykinin and cytokines. Fever is also mediated by cytokines, which increase synthesis of prostaglandin E_2.

PHARMACOKINETICS

There are 2 types of salicylic acid esters: phenolic esters (aspirin) and carboxylic acid esters (including methylsalicylate, phenylsalicylate, and glycosalicylate). Most of the studies of salicylate metabolism involve the phenolic ester aspirin, also known as acetylsalicylic acid.

Therapeutic Doses of Aspirin

Ingested salicylates are rapidly absorbed from the stomach; the pK_a of salicylate is 3.0 and approximately 50% is nonionized in the acid stomach. Absorption of salicylates may be less efficient in the small bowel because of its higher pH, but the slower rate is overcome by the large surface area of the small bowel. Plasma concentrations are achieved in 30 minutes, and maximum concentrations are often attained in less than 1 hour. Delayed absorption may result from enteric coating, salicylate-induced pylorospasm, pyloric stenosis, gastric outlet obstruction, or bezoar formation. The volume of distribution is 0.2 L/kg and 80–90% is protein bound. Salicylates are conjugated with glycine and glucuronides in the liver, and eliminated by the kidneys. Approximately 10% of salicylates are excreted in the urine as free salicylic acid, 75% as salicyluric acid, 10% as salicylic phenolic glucuronides, 5% as acylglucuronides, and 1% as gentisic acid. Free salicylic acid is filtered through the glomerulus, reabsorbed from the proximal tubules, and secreted from the proximal tubules.

Toxic Doses of Aspirin

In overdosage, peak serum concentrations may not be reached for 4–6 hours or longer. Protein (albumin) binding decreases from 90% at therapeutic con-

centrations to less than 75% at toxic concentrations because of saturation. This increases the apparent volume of distribution from 0.2 L/kg at low concentrations to more than 0.3 L/kg (possibly as high as 0.5 L/kg) at higher concentrations. As the concentration of salicylates increases, 2 of the 5 pathways of elimination—those for salicyluric acid and the salicylic phenolic glucuronide—become saturated and exhibit zero-order kinetics. As a result of this saturation, overall salicylate elimination changes from first-order kinetics to zero-order kinetics.

Topical salicylates are only rarely responsible for salicylate poisoning, as absorption through normal skin is very slow. Methylsalicylate is rapidly absorbed from the gastrointestinal tract and much, but not all, of the ester is rapidly hydrolyzed to free salicylates. When ingested, 1 mL of 98% methylsalicylate is as potent as 1.4 g of acetylsalicylic acid.

CLINICAL MANIFESTATIONS

Salicylates stimulate the respiratory center, leading to hyperventilation and respiratory alkalosis. In addition, they are weak acids and impair renal function, which leads to accumulation of inorganic acids. Salicylates also interfere with the Krebs cycle and uncouple oxidative phosphorylation, resulting in lactic acidemia and the generation of heat. Finally, the induction of fatty acid metabolism generates ketone bodies. The net result of these metabolic processes is a wide anion gap metabolic acidosis.

Although the metabolic acidosis develops in the earliest stages of toxicity, a primary respiratory alkalosis predominates initially. It is important to understand that the respiratory alkalosis of salicylate poisoning is not merely compensatory for the metabolic acidosis, but that acutely poisoned adults characteristically present with two primary acid–base disturbances. In contrast, because of limited respiratory reserve, children typically present to the hospital with a metabolic acidosis and a respiratory alkalosis, but are acidemic. Ultimately, both adults and children can develop a respiratory acidosis.

Salicylate poisoning produces a discordance between plasma and cerebrospinal fluid (CSF) glucose concentrations. Despite a normal plasma glucose, CSF glucose may be low. Hepatic glycogen stores decrease and lactate increases, suggesting that increased glycolysis partially compensates for uncoupling of oxidative phosphorylation. These increased metabolic demands stimulate peripheral lipolysis and produce ketosis.

Toxic doses of salicylates first stimulate and then depress the central nervous system. Confusion, dizziness, delirium, psychosis, and, ultimately, stupor and coma can occur. Tinnitus followed by mild to moderate reversible hearing loss typically occurs with serum salicylate concentrations of 20–45 mg/dL.

The major pulmonary effect of salicylate poisoning is acute lung injury. Gastrointestinal manifestations of salicylate use include nausea and vomiting, which probably result from local gastric irritation at lower doses and from stimulation of the medullary chemoreceptor trigger zone at higher doses. Hemorrhagic gastritis, decreased gastric motility, and pylorospasm also result from the direct gastric irritant effects of salicylates. The kidneys play a major role in the handling and excretion of salicylates. Aspirin doses >300 mg/kg can cause acute renal failure, and chronic aspirin poisoning can cause reversible or irreversible acute renal failure. Most commonly, prerenal azotemia results from volume losses and interferes with the excretion of inorganic and

organic acids. Hematologic effects of salicylate poisoning include hypoprothrombinemia and platelet dysfunction. Hyperthermia is probably the result of the dissipation of heat and energy from uncoupling oxidative phosphorylation. Paratonia, characterized by extreme muscle rigidity, is probably related to the extreme depletion of adenosine triphosphate (ATP) and the inability of the muscle fibers to relax.

Chronic Toxicity

Chronic salicylate poisoning most typically occurs in the elderly as a result of unintentional overdosing on salicylates used to treat chronic conditions such as rheumatoid arthritis or osteoarthritis. Presenting signs and symptoms of *chronic* salicylate poisoning include hearing loss and tinnitus; nausea; vomiting; dyspnea and hyperventilation; tachycardia; hyperthermia; and neurologic manifestations such as confusion, delirium, agitation, hyperactivity, slurred speech, hallucinations, seizures, and coma. Although there is considerable overlap with some of the presenting signs and symptoms of *acute* salicylate poisoning, the slow onset and less severe appearance of some of these signs of chronic poisoning in the elderly frequently cause delayed recognition of the true etiology of the patient's presentation. Typically, ill patients who suffer from chronic salicylate poisoning may be misdiagnosed as having delirium, dementia, encephalopathy of undetermined origin, diseases such as sepsis (fever of unknown origin), alcoholic ketoacidosis, respiratory failure, or cardiopulmonary disease—especially congestive heart failure, acute pulmonary edema, and even unstable angina. When diagnosis is delayed in the elderly, the morbidity and mortality associated with salicylate poisoning is high.

DIAGNOSTIC TESTING

A serum salicylate concentration is relatively easy to obtain in most hospital laboratories, although proper attention to the units reported (mg/dL vs. mg/L) is necessary. Concomitant arterial or venous blood pH values, an anion gap, and a urine analysis (for pH and ketones) are sufficient to assess the degree of toxicity.

Except in certain narrowly defined situations, the toxicity of salicylates correlates poorly with serum concentrations because the pH changes the distribution of salicylates. As such, a salicylate concentration that is associated with life-threatening toxicity in an acidemic patient may only produce minimal toxicity in an alkalemic patient. CNS (or CSF) salicylate concentrations correlate well with toxicity in animal models but are not routinely obtained. Thus the pH, anion gap, and salicylate concentrations should always be determined simultaneously and repeated frequently until the patient is stable. When the pH is unknown, a decreasing serum salicylate concentration may reflect either an increased tissue distribution with increased toxicity or an increased clearance with decreased toxicity.

MANAGEMENT

Gastric Decontamination and the Use of Activated Charcoal

In vitro studies suggest that each gram of activated charcoal can adsorb approximately 550 mg of salicylic acid. In humans, activated charcoal reduces the absorption of therapeutic aspirin doses by 50–80%. Unfortunately, be-

cause suicidal patients can easily take in excess of 20–30 g, even multiple doses of activated charcoal may be inadequate. When a recent large ingestion is suspected, orogastric lavage should be performed, and either single- or multiple-dose activated charcoal should follow. Whole-bowel irrigation with polyethylene glycol-electrolyte solution should be considered when enteric-coated or sustained-release products are ingested.

Fluid losses from salicylate poisoning are prominent and can be attributed to tachypnea, vomiting, fever, a hypermetabolic state, hyperpnea, insensible perspiration, and an increased solute load delivered to the kidney resulting in diuresis. For all of these reasons, the patient's volume status must be adequately assessed and corrected if necessary, along with any glucose and electrolyte abnormalities. A central venous pressure monitor may be required in the elderly, patients with acute lung injury, and those with a history of congestive heart failure. Increasing fluids beyond restoration of fluid balance to achieve a forced diuresis has no practical benefit.

Because salicylic acid is a weak acid (pK_a 3.0) it is ionized in an alkaline milieu and can theoretically be "trapped" there. Alkalinization of the blood with $NaHCO_3$ can keep salicylates from entering the brain and alkalinization of the urine (defined as a pH ≥7.5) enhances urinary salicylate excretion (Fig. 35–1). Alkalinizing the urine from a pH of 5 to 8 logarithmically increases renal salicylate clearance. Acetazolamide should never be used because the alkaline urine that results is tied to a systemic acidemia that shifts salicylate into the brain.

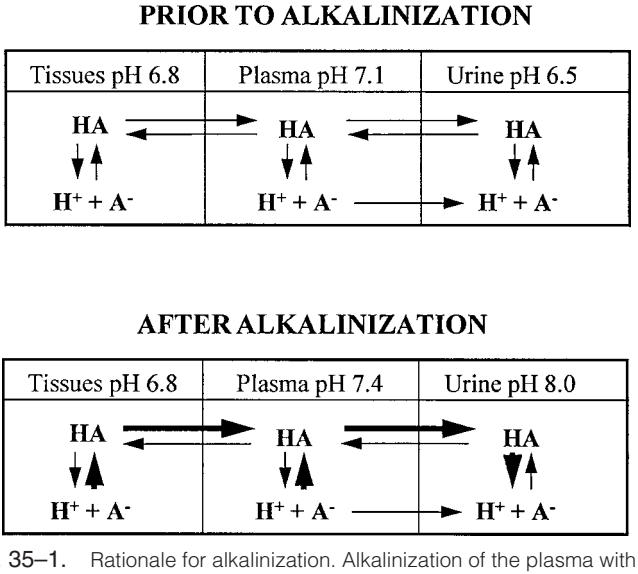

FIG. 35–1. Rationale for alkalinization. Alkalinization of the plasma with respect to the tissues and alkalinization of the urine with respect to plasma shifts the equilibrium to the plasma and urine and away from the tissues (including the brain). This equilibrium shift results in "ion trapping." *(Adapted with permission from Temple AR: Acute and chronic effects of aspirin toxicity and their treatment. Arch Intern Med 1981;141:367.)*

Alkalinization is generally achieved with a bolus of 1–2 mEq/kg of hypertonic sodium bicarbonate, followed by an intravenous infusion of 3 ampules of $NaHCO_3$ (132 mEq) in 1 L of 5% dextrose in water (D_5W), to run at 1.5–2 times maintenance fluid range. Urine pH must be maintained at 7.5–8.0 and hypokalemia must be corrected, as hypokalemia produces acid urine. Alkalinization is generally considered in any patient with tinnitus or CNS symptoms, and in all patients with salicylate concentrations greater than 30–40 mg/dL. Early hemodialysis must be considered when a patient cannot tolerate the increased solute load that results from alkalinization because of congestive heart failure, renal failure, or cerebral edema. But even when the decision has been made to hemodialyze a patient, alkalinization, when possible, helps to achieve a more rapid initial reduction in blood levels.

Endotracheal intubation followed by assisted ventilation of a salicylate-poisoned patient poses particular risks and may contribute to mortality. The greatest concern is a failure to maintain very high preintubation minute ventilation rates. As ventilation decreases, pH decreases and salicylate is rapidly transported into the brain. Death, presumably from this effect, has occurred following sedation during initial airway management.

Extracorporeal Elimination

Extracorporeal measures are indicated if the patient is very ill, has a very high serum salicylate concentration (>100 mg/dL), has severe fluid or electrolyte disturbances, or is unable to eliminate the salicylates. In most instances of severe salicylate poisoning, hemodialysis is the technique of choice, not only to clear the drug, but also to rapidly correct fluid, electrolyte, and acid–base disorders that will not be corrected by hemoperfusion alone. The combination of hemodialysis and hemoperfusion in series is feasible and may theoretically be useful for treating severe or mixed overdoses, but is rarely used. Although peritoneal dialysis has no role, continuous venovenous hemodiafiltration (CVVHD) can be considered for patients too unstable to undergo hemodialysis or in situations where hemodialysis is unavailable. In small children, exchange transfusion is a viable alternative when hemodialysis is technically difficult or unavailable.

Sodium Bicarbonate

Sodium bicarbonate ($NaHCO_3$) is a nonspecific antidote effective in the treatment of a variety of poisonings by means of a number of distinct mechanisms. It is most commonly employed to reverse the cardiotoxicity of xenobiotics that block sodium channels, enhance the elimination of weak acids by trapping them in the urine, and to correct life-threatening acidosis generated from toxic alcohols. The use of sodium bicarbonate in the treatment of rhabdomyolysis, lactic acidosis, cardiac resuscitation, and diabetic ketoacidosis is not the focus of this Antidote in Brief.

ALTERED DRUG IONIZATION RESULTING IN ALTERED DRUG DISTRIBUTION

Tricyclic Antidepressants

Sodium bicarbonate can reverse the cardiotoxic effects of the tricyclic antidepressants (TCAs) and other type IA and type IC antidysrhythmics. The similarities in electrocardiographic findings between hyperkalemia and quinidine toxicity (ie, QRS widening), led early investigators to use sodium lactate (which is metabolized to sodium bicarbonate) for the treatment of quinidine toxicity. In dogs, quinidine-induced electrocardiographic changes and hypotension were consistently reversed by the infusion of sodium lactate. When the use of sodium lactate was extended to the TCAs, a decrease in mortality from 15% to less than 3% resulted.

Experimental evidence suggests that sodium bicarbonate seems to work independently of initial blood pH, even in the setting of alkalemia, and that other methods of alkalinization, including hyperventilation and a nonsodium buffer, tris(hydroxymethyl) aminomethane (THAM), are also effective. However, sodium bicarbonate is superior to hyperventilation, hypertonic sodium chloride, and lidocaine.

Alterations in protein binding were once thought to be responsible for the effects of sodium bicarbonate. However, current data support direct and indirect improvement of sodium channels resulting in partial reversal of fast sodium channel blockade. This decreases QRS prolongation and reduces life-threatening cardiovascular toxicity such as ventricular dysrhythmias and hypotension. There is both a pH-dependent effect and a sodium-dependent effect. The pH-dependent effect increases the fraction of the more freely diffusible nonionized drug. Because it is estimated that 90% of the block is caused by the ionized form, increasing the nonionized fraction makes less drug available to bind to the sodium channel. The sodium-dependent effect increases the availability of sodium ions to pass through the open channels.

Prospective validation of treatment criteria for the use of sodium bicarbonate after TCA overdose has not been performed. The most common indications are conduction delays manifested by QRS >0.10 seconds, $R_{avr} \geq 3$ mm, or right bundle-branch block, wide-complex tachydysrhythmias, and hypotension. Because there is a critical threshold QRS duration at which ventricular dysrhythmias may occur (≥0.16 seconds), it seems reasonable that narrowing the QRS

interval may prevent the development of dysrhythmias. Although sodium bicarbonate has no proven efficacy in either the treatment or prophylaxis of TCA-induced seizures, seizures often cause acidemia, which rapidly increases the risks of conduction disturbances and ventricular dysrhythmias.

Administering sodium bicarbonate in situations in which the QRS duration is >0.10 seconds or greater may establish a theoretical margin of safety, in the event that the patient suddenly deteriorates, without adding significant demonstrable risk. In situations in which the QRS duration is less than 0.10 seconds (given the negligible risk of seizures or dysrhythmias), prophylactic use of sodium bicarbonate is not indicated.

The most commonly used preparations are an 8.4% solution (1 M), containing 1 mEq each of sodium and bicarbonate ions per milliliter (calculated osmolarity of 2000 mOsm/L) and a 7.5% solution, containing 0.892 mEq each of sodium and bicarbonate ions per milliliter (calculated osmolarity of 1786 mOsm/L). Fifty-milliliter ampules of the 8.4% and 7.5% solutions contain 50 mEq and 44.6 mEq of $NaHCO_3$, respectively. One to 2 mEq of sodium bicarbonate per kg body weight should be administered intravenously as a bolus over a period of 1–2 minutes. Greater amounts may be required to treat unstable ventricular dysrhythmias. Sodium bicarbonate can then be repeated as needed to achieve a blood pH of 7.50–7.55. The end point of treatment is a narrowing of the QRS interval. Excessive alkalemia (pH >7.55) and hypernatremia should be avoided. Because sodium bicarbonate has a brief duration of effect, a continuous infusion is usually required after the intravenous bolus. Three 50-mL ampules should be placed in 1 L of 5% dextrose in water (D_5W) and run at twice maintenance with frequent checks of QRS and pH, depending on the fluid requirements and blood pressure of the patient. Frequent evaluation of fluid status should also be performed to avoid precipitating pulmonary edema. Optimal duration of therapy has not been established. Sodium bicarbonate infusion is usually discontinued once there is improvement in hemodynamics, cardiac conduction, and resolution in altered mental status, although controlled data supporting such an approach are lacking.

Other Sodium Channel Blocking Drugs

Sodium bicarbonate is useful in treating cardiotoxicity from other drugs with sodium channel blocking effects manifested by widened QRS complexes, dysrhythmias, and hypotension. The utility of sodium bicarbonate in treating toxicity from types IA and IC antidysrhythmics, diphenhydramine, propoxyphene, amantadine, cocaine, phenothiazines, thioridazine, mesoridazine, carbamazepine, and quinine is demonstrated.

ALTERED DRUG IONIZATION RESULTING IN ENHANCED ELIMINATION

Salicylates

Judicious use of sodium bicarbonate is an essential treatment modality of salicylism. Sodium bicarbonate, through its ability to change the concentration gradient of the ionized and nonionized fractions of salicylates, is useful in decreasing tissue (eg, brain) concentrations of salicylates and in enhancing urinary elimination of salicylates.

Salicylate is a weak acid with a pK_a of 3.0. As pH increases, more of the drug is in the ionized form. Ionized molecules penetrate lipid-soluble mem-

branes less rapidly than nonionized molecules because of the presence of polar groups on the ionized form. Consequently, weak acids, such as salicylates, may accumulate in an alkaline milieu, such as an alkaline urine, when the ionized forms predominate.

Increasing the serum pH in patients with severe salicylism is essential to protect the brain from a lethal CNS salicylate burden. In experimental models, lowering the blood pH produces a shift of salicylate into the tissues, and raising the pH is protective. Enhancing the urinary elimination of salicylate by trapping ionized salicylate in the urine also provides great benefit. The exact mechanism of pH-dependent salicylate elimination has generated controversy. The pH-dependent increase in urinary elimination was initially ascribed to "ion trapping": the filtering of both ionized and nonionized salicylate, while reabsorbing only the nonionized salicylate. Because the quantitative difference between the percentage of molecules trapped in the ionized form at a pH of 5.0 (99% ionized) and a pH of 8.0 (99.999% ionized) is small, decreases in tubular reabsorption cannot fully explain the rapid increase in urinary elimination seen above a pH of 7.0. The Fick law of diffusion states that the rate of flow of a diffusing substance is proportional to its concentration gradient. A large concentration gradient between the nonionized salicylate in the peritubular fluid (and blood) and the tubular luminal fluid is found in alkaline urine. Hence, increased tubular diffusion, not decreased reabsorption, probably accounts for most of the increase in salicylate elimination observed in the alkaline urine.

Sodium bicarbonate is indicated in the treatment of salicylate poisoning for most patients with evidence of significant systemic toxicity. Although some authors suggest alkali therapy for asymptomatic patients with concentrations greater than 30 mg/dL, there are limited data to support this approach. For patients suffering from chronic poisoning, concentrations are not as helpful and may be misleading; clinical criteria remain the best indicators for therapy. Patients with contraindications to sodium bicarbonate use, such as renal failure or acute lung injury, should be considered candidates for hemodialysis.

Dosing recommendations depend on the acid–base status of the patient. For the patient with acidemia, rapid correction is indicated with intravenous administration of 1–2 mEq/kg body weight of sodium bicarbonate. Once the blood is alkalinized, or if the patient has already presented with an alkalemia, continued titration with sodium bicarbonate is recommended until the urine pH reaches 7.5–8.0. Alkalinization can be maintained with a continuous sodium bicarbonate infusion of 100–150 mEq in 1 L of D_5W at 150–200 mL/h (or about twice the maintenance requirements in a child). Hypokalemia can make urinary alkalinization particularly problematic, as the kidney will secrete hydrogen ions into the urine in an attempt to resorb potassium. Thus to alkalinize the urine, appropriate potassium supplementation to achieve normokalemia may be required.

Phenobarbital

Although cardiopulmonary support is the most critical intervention in the treatment of patients with severe phenobarbital overdose, sodium bicarbonate may be a useful adjunct to the general supportive care. Phenobarbital is a weak acid (pK_a 7.24) that undergoes significant renal elimination. As in the case of salicylates, alkalinization of the blood and urine can reduce the severity and duration of toxicity. Given the relatively high pK_a of phenobarbital,

significant phenobarbital accumulation in the urine is evident only when urinary pH is raised above 7.5. As the pH approaches 8.0, a 3-fold increase in urinary elimination occurs. In a human volunteer study, urinary alkalinization with sodium bicarbonate was associated with a decrease in phenobarbital elimination half-life from 148 hours to 47 hours. However, this beneficial effect was less than the effect achieved by multiple-dose activated charcoal (MDAC), which reduced the half-life to 19 hours.

Sodium bicarbonate therapy does not appear warranted in the treatment of ingestions of other barbiturates, such as pentobarbital and secobarbital, each of which has a pKa above 8.0 and is predominantly eliminated by the liver.

Chlorpropamide

Chlorpropamide is a weak acid (pK_a 4.8) with a long half-life (30–50 hours). In a human study using therapeutic doses of chlorpropamide, urinary alkalinization with sodium bicarbonate significantly increased renal clearance of the drug. Alkalinization reduced the elimination half-life from 50 hours to 13 hours.

Chlorophenoxy Herbicides

Alkalinization is indicated in the treatment of poisonings from the weed killers that contain chlorophenoxy compounds, such as 2,4-dichlorophenoxyacetic acid (2,4-D), or 2,4-chloro-2-methylphenoxy propionic acid (MCPP). These compounds are weak acids (pK_a of 2.6 and 3.8 for 2,4-D and MCPP, respectively) that are excreted largely unchanged in the urine. In an uncontrolled case series of 41 patients poisoned with a variety of chlorophenoxy herbicides, 19 of whom received sodium bicarbonate, alkaline diuresis significantly reduced the half-life of each compound by enhancing renal elimination.

CORRECTING METABOLIC ACIDOSIS

Toxic Alcohols

Sodium bicarbonate has two important roles in treating toxic alcohol ingestions. As an immediate temporizing measure, administration of sodium bicarbonate may reverse the life-threatening acidemia associated with methanol and ethylene glycol ingestions. Also the proportion of ionized formic acid can be increased by administering bicarbonate, thereby trapping formate in the blood compartment. Consequently, decreased visual toxicity may result from the prevention of the entry of the toxic metabolite into the eye. Sodium bicarbonate decreases tissue penetration of the formic acid and enhances urinary elimination.

Early treatment of acidemia with sodium bicarbonate is strongly recommended in cases of methanol and ethylene glycol poisoning. Sodium bicarbonate should be administrated to toxic alcohol-poisoned patients with an arterial pH below 7.30. Alkalinization is only a temporizing method and should not be considered a substitute for fomepizole, ethanol, or hemodialysis.

INCREASING DRUG SOLUBILITY

Methotrexate

Urinary alkalinization with sodium bicarbonate is routinely employed during high-dose methotrexate cancer chemotherapy therapy. Methotrexate is predom-

inantly eliminated unchanged in the urine. Because it is poorly water soluble in acidic urine, tubular precipitation of methotrexate may occur, leading to nephrotoxicity and decreased elimination, increasing the likelihood of methotrexate toxicity. The administration of sodium bicarbonate (as well as intensive hydration) increases methotrexate solubility and subsequent elimination.

NEUTRALIZATION

Chlorine Gas

Nebulized sodium bicarbonate serves as a useful adjunct in the treatment of pulmonary injuries resulting from chlorine gas inhalation. Inhaled sodium bicarbonate neutralizes the hydrochloric acid that is formed when the chlorine gas reacts with the water in the respiratory tree. In a chlorine-inhalation sheep model, animals treated with 4% nebulized sodium bicarbonate solution demonstrated higher PO_2 and lower PCO_2 than did the normal saline-treated animals. Anecdotal experience suggests that nebulized bicarbonate therapy may lead to improvement of symptoms in humans.

REDUCTION IN FREE RADICAL FORMATION

Contrast Media

A recent study suggests that sodium bicarbonate might also be beneficial in preventing contrast-induced nephropathy. A randomized trial on 119 patients compared an infusion of 154 mEq/L of either sodium bicarbonate or sodium chloride before (3 mL/kg for 1 hour) and after (1 mL/kg/h for 6 hours) iopamidol administration. Contrast-induced nephropathy occurred in 8 patients in the sodium chloride group and in 1 patient in the sodium bicarbonate group.

36 Nonsteroidal Antiinflammatory Agents

HISTORY AND EPIDEMIOLOGY

Nonsteroidal antiinflammatory drugs (NSAIDs) are a heterogeneous group of chemicals that share similar therapeutic properties. NSAIDs have analgesic, antipyretic, and antiinflammatory effects. Ibuprofen was first introduced in the United States in 1974 and was approved for nonprescription use in 1984. Like ibuprofen, the first-generation NSAIDs inhibit cyclooxygenase (COX) in a nonselective fashion. With the realization that COX inhibition could be separated into COX-1 and COX-2, and that most of the adverse gastrointestinal (GI) effects were mediated by COX-1, selective COX-2 inhibitors were introduced and marketed as having less GI toxicity than the older, less selective NSAIDs. In the fall of 2004, the manufacturer of Vioxx (rofecoxib), a COX-2 inhibitor, voluntarily withdrew it from sale when it was discovered that there was an increased cardiovascular mortality associated with its use. In April 2005, the FDA findings led the manufacturer of Bextra to withdraw that COX-2 inhibitor from the market, leaving Celebrex (celecoxib) as the only selective COX-2 inhibitor available in the United States.

Nonsteroidal exposures are increasingly common, accounting for more than 3% of all cases reported to poison centers in the United States. Reported deaths are extremely uncommon.

PHARMACOLOGY

The NSAIDs competitively inhibit COX, which produces both the therapeutic and adverse effects of this group of drugs. COX-1 is present in the kidney and GI tract and is responsible for vascular hemostasis, GI wall integrity, and renal homeostasis. Inhibition of COX-1 decreases synthesis of thromboxane A_2 in platelets and interferes with their aggregation. COX-2 is induced by inflammatory mediators and produces prostaglandins at the site of inflammation, which are responsible for mediating vasodilation, increasing vascular permeability, and sensitizing pain fibers. Inhibition of COX-2 is associated with both the analgesic and antiinflammatory actions of the NSAIDs, without antiplatelet effects.

PHARMACOKINETICS AND TOXICOKINETICS

NSAIDs are rapidly absorbed from the GI tract, with peak levels occurring within 2 hours. Large ingestions delay peak concentrations to 3–4 hours after the ingestion. They are all weakly acidic and highly protein bound (>90%), with volumes of distribution of approximately 0.1–0.2 L/kg. Hepatic metabolism is the primary route for NSAID elimination, with renal elimination of unchanged drug accounting for less than 10% of clearance (except indomethacin with 10–20%). The elimination half-life for the majority of NSAIDs is less than 8 hours; however, the half-lives of diflunisal, nabumetone, naproxen, and sulindac are between 8 and 30 hours, and the half-lives of phenylbutazone and piroxicam are 30 hours.

PATHOPHYSIOLOGY

Table 36–1 summarizes the adverse effects associated with NSAIDs. Many of the adverse effects, and probably all or most of the acute toxicities of the NSAIDs, are associated primarily with the inhibition of COX-1. However, the high anion gap acidosis that occurs infrequently with NSAID overdose theoretically results from formation of NSAID metabolites that are weak acids, hypotension, and relative hypoxia. There is no information to indicate that inhibition of COX itself is responsible for the production of the metabolic acidosis. There are also many clinically significant drug interactions with NSAIDs (Table 36–1).

TABLE 36–1. Selected Adverse Effects of Nonsteroidal Antiinflammatory Drugs

Gastrointestinal
- Dyspepsia
- Ulceration
- Perforation
- Hemorrhage (often painless in the elderly)
- Elevated hepatic aminotransferase concentrations (transient)
- Hepatocellular injury (rare)

Renal
- Acute renal failure
- Fluid and electrolyte retention
- Interstitial nephritis
- Nephrotic syndrome
- Papillary necrosis

Hypersensitivity/pulmonary
- Asthma exacerbation
- Anaphylactoid reaction
- Pneumonitis

Hematologic
- Increased bleeding time (nonselective COX inhibitors)
- Agranulocytosis
- Aplastic anemia
- Thrombocytopenia
- Neutropenia
- Hemolytic anemia

Central nervous system
- Headache
- Aseptic meningitis
- Delirium
- Cognitive dysfunction, especially in the elderly
- Hallucinations

Drug interactions
- Anticoagulants: NSAIDs increase risk of GI bleeding
- Antihypertensives (especially diuretics, β-adrenergic antagonists, and ACE inhibitors): NSAIDs reduce antihypertensive effects
- Sulfonylureas: NSAIDs increase hypoglycemic effect
- Lithium: NSAIDs increase risk of lithium toxicity
- Digoxin: NSAIDs increase risk of digoxin toxicity
- Aminoglycosides: NSAIDs increase risk of aminoglycoside toxicity

CLINICAL MANIFESTATIONS

Although there may be differences in severity and frequency of some clinical manifestations, the toxic effects of the different nonselective NSAIDs are generally similar in acute overdose. Clinical effects typically occur within 4 hours of ingestion. Because COX-2 receptor selectivity is lost at high concentrations, overdoses of these agents are expected to cause toxicity similar to the nonselective NSAIDs.

The most common toxic effects in acute overdose are GI distress (nausea, vomiting, epigastric pain, GI hemorrhage) and CNS depression. Other CNS effects can include changes in cognition, hallucinations, muscle twitching, and seizures, and are most frequent after mefenamic acid overdose. Muscle twitching may be focal or generalized, often progressing to grand mal seizures 2–7 hours postingestion. Seizures can occur at doses as low as 2 g of mefenamic acid in a child and 6 g (over 24 hours) in an adult.

Before its removal from the US market, phenylbutazone was associated with the majority of the severe toxicity attributed to NSAIDs. Phenylbutazone overdoses were characterized by early GI symptoms, acid–base and electrolyte disturbances, dizziness, hypotension, acute lung injury, seizures, coma, and respiratory and cardiac arrest. Acute signs were followed by renal, hepatic, and hematologic dysfunction 2–7 days after overdose. Unfortunately, phenylbutazone is still available from veterinary sources and for humans in other countries.

DIAGNOSTIC TESTING

Measurement of serum NSAID concentrations is unnecessary for the clinical assessment and management of patients with NSAID exposures. Although a nomogram is available, serum ibuprofen concentrations actually correlate poorly with clinical outcome. For the patient with an intentional ingestion, a complete blood count, prothrombin time, serum electrolytes, serum creatinine and BUN should be considered as baseline parameters. A serum pregnancy test should be obtained for women of child-bearing age. If significant respiratory or CNS toxicity is present, acid–base status should be assessed. A serum acetaminophen concentration should be obtained to determine whether there is a concurrent acetaminophen ingestion, especially in patients with a history of recent painful or febrile conditions.

MANAGEMENT

Because of rapid absorption, symptoms should be evident by 4–6 hours after ingestion. Most NSAID toxicity resolves with supportive care. Otherwise healthy patients with a history of NSAID overdose generally require only fluid and electrolyte replacement and supportive care. GI decontamination with activated charcoal should be considered only for those patients with large ingestions or suspected coingestants. Patients who present with CNS, acid–base, or cardiovascular toxicity, or who have known risk factors for organ system toxicity associated with NSAIDs, should be considered at higher risk for complications.

The high degree of protein binding characteristic of all NSAIDs makes hemodialysis ineffective in overdose, and experience with hemoperfusion is insufficient to determine its usefulness. There is no antidote for NSAID poisoning. Several therapeutic interventions have been tried to prevent the adverse

GI effects resulting from loss of cytoprotection from prostaglandins; use of proton pump inhibitors has shown some success, whereas H_2-receptor blockade is generally unsuccessful. Concurrent administration of misoprostol, a prostaglandin E analog, might also be effective in preventing GI side effects of NSAIDs. These approaches to minimizing adverse effects have not been used as treatment of NSAID overdoses.

37 Colchicine and Podophyllin

COLCHICINE

Colchicine is derived from two plants of the Liliaceae family: *Colchicum autumnale* (autumn crocus, meadow saffron, wild saffron, naked lady, son-before-the-father) and *Gloriosa superba* (glory lily). The leaves of *Colchicum autumnale* closely resemble those of the *Allium ursinum,* or wild garlic, and have been mistaken for them. The tubers of *Gloriosa superba* can be confused with *Ipomoea batatas* (sweet potatoes).

Pharmacology

Colchicine is a potent inhibitor of microtubule formation and function that interferes with cellular mitosis, intracellular transport mechanisms, and maintenance of cell structure and shape. The ubiquitous presence of microtubules in cells comprising various tissues and organs throughout the body presents a wide variety of targets for colchicine in poisoning. Colchicine accumulates in leukocytes and has inhibitory effects on their inflammatory function.

Pharmacokinetics/Toxicokinetics

Colchicine is rapidly absorbed with a bioavailability between 25% and 50%. It undergoes extensive first-pass hepatic metabolism and has a therapeutic volume of distribution between 2.2 and 12 L/kg, which in overdose, may increase to 21 L/kg. Colchicine can cross the placenta and is secreted in breast milk; however, it is not dialyzable. Postmortem examination of colchicine-poisoned patients reveals high concentrations within the bone marrow, testicle, spleen, kidney, lung, brain, and heart.

Colchicine is taken up by white and red blood cells in concentrations 5–10 times higher than serum during the first several hours after acute overdose. Peak plasma concentrations following ingestion occur between 1 and 3 hours. Toxic effects usually do not occur with concentrations less than 3 ng/mL.

Colchicine is primarily metabolized through hepatic demethylation by cytochrome P450 3A4 (CYP3A4) with up to 20% of the ingested dose excreted unchanged through the urinary system. The terminal elimination phase ranges from 1.7–30 hours. Individuals with severe renal failure and liver cirrhosis may have an elimination half-life that is prolonged up to 10-fold.

Pathophysiology

Microtubules play a vital role in cellular mitosis and possess significant dynamic instability. Xenobiotics that bind to specific regions on tubulin, the building block of microtubules, can interfere with microtubule structure and function, thereby causing mitotic and cellular dysfunction and death. Colchicine also inhibits microtubule-mediated intracellular granule transport.

Toxic Dose

The acute toxic dose for colchicine is not well established. An older case series suggested that patients with ingestions of greater than 0.8 mg/kg uni-

TABLE 37–1. Colchicine Poisoning: Common Clinical Findings

Phase	Time[a]	Signs/Symptoms
I	0–24 h	Nausea, vomiting, diarrhea
		Dehydration
		Leukocytosis
II	1–7 d	Possible risk of sudden cardiac death (24–36 h)
		Pancytopenia
		Renal failure
		Sepsis
		Acute respiratory distress syndrome
		Electrolyte imbalances
		Rhabdomyolysis
III	>7 d	Alopecia
		Myopathy, neuropathy, or myoneuropathy

[a]Interval time course is not absolute, and overlap of symptom presentation may occur.

formly died, whereas those with ingestions between 0.5 mg/kg and 0.8 mg/kg would survive if given supportive care. More recent literature suggests that severe toxicity and even death can occur with smaller doses, and that some patients may survive ingestions in excess of 0.8 mg/kg.

Clinical Presentation

The clinical findings in poisoned patients are commonly described in three phases (Table 37–1).

The hematopoietic effects of colchicine overdose are characterized by an initial peripheral leukocytosis, which is followed by a profound leukopenia, commonly associated with pancytopenia, usually beginning 48–72 hours after overdose. Sudden cardiovascular collapse may occur between 24 and 36 hours after ingestion, as a consequence of a combination of hypovolemia and direct myotoxic effects.

Neuropathy and/or myopathy result from either long-term therapy or acute poisoning with colchicine. Patients can present with proximal limb weakness, distal sensory abnormalities, distal areflexia, and nerve-conduction problems consistent with an axonal neuropathy.

Other indirect effects of colchicine are pulmonary and renal dysfunction, and virtually any organ system, including the skin, can be affected.

Diagnostic Testing

Colchicine concentrations in body fluids are not readily available in a clinically relevant fashion and have no well-established correlation to severity of illness. However, effective steady-state plasma concentrations for treatment of various illnesses are reported as 0.5–3 ng/mL. Concentrations greater than 3 ng/mL are associated with the development of toxicity. Testing for suspected or known colchicine poisoning should include routine laboratory tests and other targeted testing, as needed. Serial complete blood counts should be ordered (at least every 12 hours) to watch for the development of depression in cell lines. An electrocardiogram and chest radiograph also should be ordered.

Management

Treatment for patients with colchicine poisoning is mainly supportive, which includes intravenous fluid replacement, vasopressor use, hemodialysis (for renal failure), antibiotics for suspected secondary infection, and adjunctive respiratory therapy (endotracheal intubation, positive end-expiratory pressure), as indicated. Consultation with other specialists should be obtained as needed.

Gastrointestinal Decontamination

Because most patients with an acute oral colchicine overdose present several hours after their ingestion, vomiting has already begun and the usefulness of gastrointestinal decontamination at this time is inadequately defined. However, given the extensive morbidity and mortality associated with colchicine overdose, gastric lavage probably should be performed in patients who present within 1–2 hours of ingestion and who are not vomiting. A dose of activated charcoal should be administered following lavage, or in its place, multiple-dose activated charcoal (MDAC) should be considered because enterohepatic recirculation might occur.

Adjunctive Therapy

Granulocyte colony-stimulating factor (G-CSF) has had some success in the treatment of colchicine-induced leukopenia and thrombocytopenia. Dosing should be determined by specialists in hematology and in conjunction with the manufacturer's instructions.

Extracorporeal Elimination

Hemodialysis and hemoperfusion are not useful for eliminating colchicine, based on its large volume of distribution and large degree of plasma protein binding.

Disposition

Because of the severe morbidity and mortality associated with colchicine toxicity, all symptomatic patients with suspected or known significant overdose should be admitted to the hospital for observation. Since there is a risk of sudden cardiovascular collapse within the first 24–48 hours, intensive care unit monitoring is recommended for all symptomatic patients for at least this initial time period. All exposed patients should be observed for at least 8–12 hours. Those patients who do not manifest gastrointestinal signs and symptoms within that initial time period following ingestion are unlikely to be significantly poisoned.

PODOPHYLLUM RESIN OR PODOPHYLLIN

Podophyllin is the name often used to refer to a resin extract from the rhizomes and roots of certain plants of the genus *Podophyllum.* Podophyllum resin, or podophyllin, contains at least 16 physiologically active compounds, including podophyllotoxin. Podophyllotoxin is a potent microtubular poison, similar to colchicine, and causes analogous effects in overdose.

Podophyllin is primarily used in modern pharmacopeia as a topical treatment for verruca vulgaris and condyloma acuminatum. Poisoning usually is a result of systemic absorption following topical application, following inges-

tion of the resin or plant, and following consumption of a commercial preparation of the extract. Systemic toxicity is described after unintentional dispensing of the incorrect herb, as well as after ingestion of herbal preparations containing podophyllin.

Pharmacokinetics/Toxicokinetics

Very limited information exists regarding the pharmacokinetics of podophyllin. Podophyllotoxin is reported to be eliminated through the bile with a half-life of 48 hours, but this is unverified.

Pathophysiology

Podophyllotoxin binds to tubulin subunits and interferes with subsequent microtubule structure and function. Podophyllotoxin also inhibits fast axoplasmic transport similar to colchicine by interference with microtubule structure and function. Many other compounds, such as the vinca alkaloids, cryptophycins, and halichondrins, also inhibit microtubule polymerization in a similar manner.

Clinical Presentation

Poisoning is described following ingestion, intravenous administration, as well as after systemic absorption from topical application of podophyllin. Nausea, vomiting, abdominal pain, and diarrhea usually begin within several hours after ingestion. Symptoms of poisoning might be delayed for 12 hours or more after topical exposure to podophyllin and often are caused by improper usage (excessive topical exposure, interruption in skin integrity, or failure to remove the preparation after a short time period). Initial clinical findings are not necessarily dictated by the route of exposure.

Alterations in central and peripheral nervous system function tend to predominate in podophyllin toxicity. Patients present with, or rapidly progress to, confusion, obtundation, and coma. Delirium and both auditory and visual hallucinations have been reported during the initial presentation. Patients develop paresthesias, cranial neuropathies, and absent deep tendon reflexes. Patients who recover from the initial event are at risk of developing a peripheral sensorimotor axonopathy. The reported duration for recovery from podophyllin-induced axonopathy is variable but can take several months.

Hematologic toxicity from podophyllin most likely results from its antimitotic effects in a manner similar to colchicine, but is not nearly as consistent in its pattern, severity, and frequency.

Diagnostic Testing

Podophyllin or podophyllotoxin concentrations are not readily available. Routine testing for suspected or known podophyllin poisoning should include routine laboratory tests and other targeted testing, as needed. Serial complete blood counts should be obtained in cases of poisoning to detect pancytopenia. An electrocardiogram and chest radiograph also should be ordered.

Management

Management primarily consists of supportive and symptomatic care. Gastric lavage should be considered if presentation occurs within 1 hour of ingestion.

If the patient presents within 1–2 hours of ingestion, a dose of activated charcoal should be given. Any topically applied podophyllin should be thoroughly removed. Supportive and symptomatic care should be instituted, as needed. The benefit of resin or charcoal hemoperfusion is unclear, although the use is reported.

Disposition

Significant ingestions of podophyllin can result in gastrointestinal symptoms within a few hours, but patients also can present with primarily neurologic symptoms, such as confusion or obtundation. Patients probably should be observed for toxicity for at least 12 hours after ingestion, and perhaps even longer after a significant dermal exposure.

38 | Opioids

HISTORY AND EPIDEMIOLOGY

Opioids find their widest clinical application in the relief of acute or chronic pain. Opioids are available in various formulations that allow administration by virtually any route. The terminology used in this chapter recognizes the broad range of agents commonly considered to be opiumlike. The term *opiate* specifically refers to the relevant alkaloids that are derived directly from the opium poppy: morphine, codeine, and, to some extent, thebaine and noscapine. *Opioids* are a much broader class of agents that are capable of producing either opiumlike effects or of binding to opioid receptors (detailed below). A *semisynthetic opioid*, such as heroin or oxycodone, is created by the chemical modification of an opiate. Alternatively, a *synthetic opioid* is a chemical compound, not derived from an opiate, which is capable of binding to an opioid receptor and producing opioid effects clinically. The term *narcotic* refers to a sleep-inducing xenobiotic and was initially used to connote the opioids. In its current use, however, law enforcement and the public use the term to indicate any illicit psychoactive substance.

PHARMACOLOGY

Opioid Receptor Subtypes

There are three categories of opioid-receptor subtypes, each having several subtypes that are primarily responsible for specific clinical effects (Table 38–1).

Mu Receptor (μ, MOP or OP_3)

Nearly all of the recognized endogenous opioids have some affinity for the μ receptor although none is selective for it. There are two well-defined subtypes (μ_1 and μ_2), although there are currently no opioids with sufficient selectivity to make this dichotomy clinically relevant.

Kappa Receptor (κ, KOP or OP_2)

Kappa receptors exist predominantly in the spinal cord of higher animals, although they are also found both in the antinociceptive regions of the brain and in the substantia nigra. Stimulation is responsible for spinal analgesia, miosis, and diuresis (via inhibition of antidiuretic hormone [ADH] release). Unlike μ, however, κ-receptor stimulation is not associated with significant respiratory depression or constipation.

Delta Receptor (δ, DOP or OP_1)

Little is known about δ receptors, although the enkephalins are their endogenous ligands.

Nociceptin/Orphanin FQ Receptor (ORL_1 or OP_4)

The ORL_1 receptor was identified in 1994, based on sequence homology during screening for opioid receptor genes with DNA libraries. A clinical role has yet to be defined, but anxiolytic and analgesic properties are described.

TABLE 38–1. Clinical Effects Related to Opioid Receptors

1996 Conventional Name	Proposed IUPHAR Name[a]	IUPHAR Name[a]	Important Clinical or Receptor Agonists Effects
μ_1	OP_{3a}	MOP	Supraspinal analgesia Peripheral analgesia Sedation Euphoria Prolactin release
μ_2	OP_{3b}		Spinal analgesia Respiratory depression Physical dependence Gastrointestinal dysmotility Pruritus Bradycardia Growth hormone release
κ_1	OP_{2a}	KOP	Spinal analgesia Miosis Diuresis
κ_2	OP_{2b}		Psychotomimesis Dysphoria
κ_3	OP_{2b}		Supraspinal analgesia
δ	OP_1	DOP	Spinal and supraspinal analgesia Modulation of μ-receptor function Inhibit release of dopamine
Nociceptin/ orphanin FQ	OP_4	NOP	Anxiolysis Analgesia

[a]International Union of Pharmacology Committee on Receptor Nomenclature.

Sigma Receptor (σ)

Although originally conceived as an opioid subtype, the σ receptor is no longer considered to be opioid in character, and has not been given a designation.

Opioid-Receptor Signal Transduction Mechanisms

Figure 38–1 illustrates opioid receptor signal transduction mechanisms. Continuing research into the mechanisms by which an opioid receptor induces an effect has produced confusing, and often contradictory, results. Despite the initial theory that each receptor subtype was linked to a specific transduction mechanism, individual receptor subtypes may use one or more mechanisms, depending on several factors, including receptor localization (eg, presynaptic vs postsynaptic).

CLINICAL MANIFESTATIONS

Therapeutic Effects

Analgesia

Although classical teaching attributes opioid analgesia solely to the brain, opioids actually appear to modulate cerebral cortical pain perception at su-

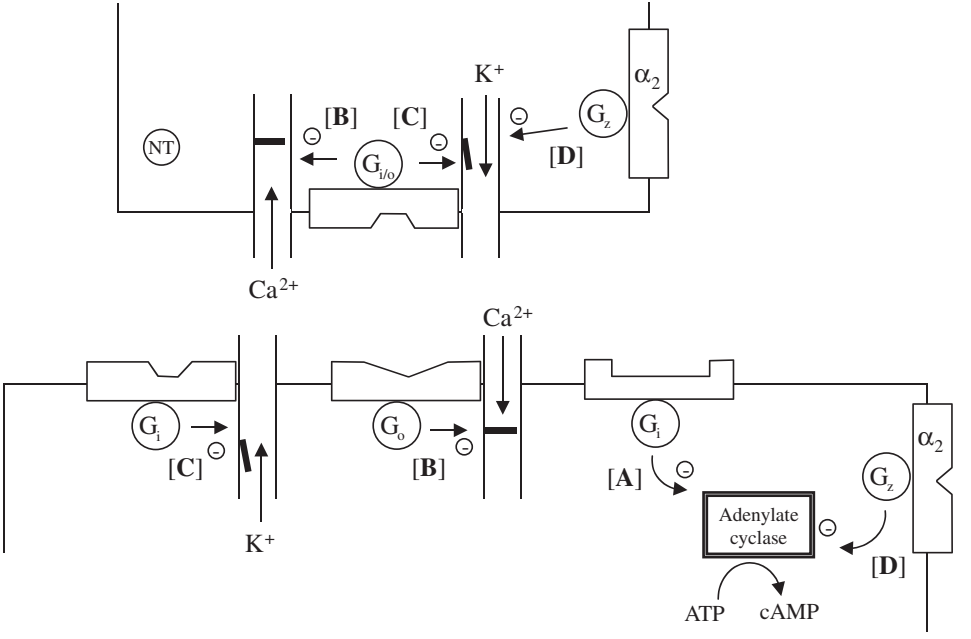

FIG. 38–1. Opioid-receptor signal transduction mechanisms. Upon binding of an opioid agonist to an opioid receptor, the respective G protein is activated. G proteins may **(A)** reduce the capacity of adenylate cyclase to produce cyclic adenosine monophosphate (cAMP); **(B)** close calcium channels that reduce the signal to release neurotransmitters; **(C)** open potassium channels and hyperpolarize the cell, which indirectly reduces cell activity. Each mechanism has been found coupled to each receptor subtype, depending on location of the receptor (pre-/postsynaptic), and the neuron within the brain. Note that α_2 receptors **(D)** mediate similar effects, using a different G protein (G_z). NT = neurotransmitter.

praspinal, spinal, and peripheral levels. The μ-opioid receptor is primarily responsible and is found in the brain, spinal cord, and peripherally (eg, joints).

Delta and κ receptors are responsible for mediation of analgesia as well, but they exert their analgesic effect predominantly in the spinal cord. Conceptually, these receptors modulate nociceptive impulses in transit to the thalamus via the spinothalamic tract to reduce the perception of the pain by the brain. Agonist–antagonists, with agonist affinity for the κ receptor and antagonist effects at the μ receptor, maintain analgesic efficacy.

Reluctance to use opioids for analgesia often stems from the fear that patients may develop dependency or abuse. However, despite extensive investigation, this concern remains unfounded. Furthermore, opioid analgesics are often better tolerated, safer, and less expensive than the alternatives, such as the nonsteroidal antiinflammatory drugs.

Euphoria

The pleasurable effects of many of the drugs used by humans are mediated by the release of dopamine in the mesolimbic system. This final common pathway is shared by all opioids that activate the μ-/δ-receptor complex.

Exogenous opioids do not induce uniform psychological effects. Some, particularly the highly lipophilic xenobiotics such as heroin, are euphorigenic, whereas morphine is largely devoid of such pleasurable effects. Morphine administration, however, results in analgesia, anxiolysis, and sedation. Because heroin has little affinity for opioid receptors and must be deacetylated to 6-monoacetylmorphine and morphine for effect, it is likely that these seemingly incompatible properties relate to pharmacokinetic differences in blood–brain barrier penetration. Fentanyl produces effects that are noted to be subjectively similar to heroin by chronic users.

Antitussive

Codeine and dextromethorphan are two opioids with cough-suppressant activity. It is unlikely that cough suppression is mediated via the μ_1-opioid receptor because the ability of other opioids to suppress the medullary cough centers is not correlated with their analgesic effect. Agonism of the μ_2- or κ-opioid receptors and antagonism of the δ-opioid receptor are often the suggested mechanism.

Clinically Significant Toxic Effects

When used correctly for medical purposes, opioids are remarkably safe and effective. However, excessive dosing for any reason may result in serious toxicity. Most adverse or toxic effects are predictable based on "opioid" pharmacodynamics (eg, respiratory depression), although several opioids produce unexpected "nonopioid" or xenobiotic-specific responses. Notwithstanding some minor variations, patients poisoned by all available opioids predictably develop a constellation of signs known as the opioid toxic syndrome (Chap. 3); mental status depression, hypoventilation, miosis, and reduced bowel motility are the classical elements (Table 38–2).

Respiratory Depression

Experimentally, using various opioid agonists and antagonists, μ_2 receptors are consistently implicated in the respiratory depressant effects of morphine. Through these receptors, opioid agonists reduce ventilation by diminishing

TABLE 38–2. Clinical Effects of Opioids

Cardiovascular	Peripheral vasodilation
	Orthostatic hypotension
	Bradycardia
Dermatologic	Flushing (histamine)
	Pruritus
Endocrinologic	Reduced ADH release
	Reduced gonadotrophin release
Gastrointestinal	Reduced motility
	Reduced gastric acid secretion
	Increased biliary tract pressure
	Increased anal sphincter tone
Neurologic	Sedation, coma
	Analgesia
	Euphoria
	Seizures (meperidine, propoxyphene)
	Antitussive
Ophthalmic	Miosis
Pulmonary	Respiratory depression
	Bronchospasm (histamine)
	Acute lung injury

the sensitivity of the medullary chemoreceptors to hypercapnia. In addition to the loss of hypercarbic stimulation, opioids also depress the ventilatory response to hypoxia. The combined loss of hypercarbic and hypoxic drive leaves virtually no stimulus to breathe and apnea follows. Among most available opioid agonists, equianalgesic doses produce approximately the same degree of respiratory depression. Patients chronically exposed to opioid agonists, may develop partial tolerance to the respiratory depressant effects of opioid agonists. Ventilatory depression may be secondary to either a reduction in ventilatory rate or in tidal volume, suggesting that measurement of only the ventilatory rate may not be adequate to detect hypoventilation.

Acute Lung Injury

Virtually all opioids are implicated, and opioid-related acute lung injury is reported in diverse clinical situations. Typically, the patient regains normal ventilation following a period of profound respiratory depression, either spontaneously or following the administration of an opioid antagonist, and over the subsequent several minutes to hours develops hypoxemia, pulmonary rales, and frothy, pink sputum. No single mechanism can be consistently invoked in the genesis of opioid-associated acute lung injury, although both hypoxic alveolar damage and negative-pressure barotrauma (inspiring against a closed glottis) are widely accepted. The relationship of acute lung injury to naloxone appears to be similar to "neurogenic" pulmonary edema, in which massive sympathetic discharge from the central nervous system occurs and produces "cardiogenic" pulmonary edema from the acute effects of catecholamines on the myocardium.

Cardiovascular

Arteriolar and venous dilation secondary to opioid use may result in mild reduction in blood pressure, an effect that is likely histamine-mediated. Prominent cardiovascular toxicity may occur with the use of propoxyphene, which causes wide-complex dysrhythmias and negative contractility through sodium channel

antagonism. Certain opioids at therapeutic concentrations, particularly methadone, can interfere with normal cardiac repolarization and produce QTc prolongation, an effect that predisposes to the development of torsades de pointes.

Seizures

Seizures are a rare complication of the therapeutic use of most opioids. In patients with acute opioid overdose, seizures are most likely to be caused by hypoxia. However, seizures should be anticipated in patients with meperidine, propoxyphene, or tramadol toxicity.

DIAGNOSTIC TESTING

Laboratory Considerations

Because opioids may be chemically detectable long after their clinical effects have dissipated, assay results cannot be considered in isolation, but rather viewed in the clinical context. Use of the clinical history and physical examination, occasionally with the response to naloxone, is generally sufficient for diagnostic purposes. In the acute care setting, the slow laboratory turnaround time further limits the usefulness of opioid assays.

Cross-Reactivity

Because most clinical assays depend on structural features to identify a drug, structurally similar opioids may be detected in lieu of the desired drug. Whether a similar drug is noted by the assay depends on the sensitivity and specificity of the assay used, as well as the serum concentration. The typical opioid assay identifies morphine, explaining why opioids that are derived or structurally similar to morphine are most likely to cross react.

Congeners and Adulterants

Commercial opioid assays, which are specific for morphine, are unlikely to detect most of the semisynthetic and synthetic opioids. For example fentanyl, a very potent opioid frequently responsible for opioid epidemic deaths, does not cross react with the morphine assay initially masking its involvement in these fatalities until specific testing is performed.

MANAGEMENT

Hypoglycemia, hypoxia, and hypothermia are common clinical presentations that share features with opioid poisoning and may exist concomitantly. Each may be rapidly diagnosed with routinely available, real-time testing, but the proof of their existence does not exclude opioid toxicity. Other drugs responsible for similar clinical presentations include clonidine, phencyclidine (PCP), phenothiazines, and sedative-hypnotics, primarily benzodiazepines. In such patients, however, clinical evidence is usually available to assist in diagnosis. Most difficult to differentiate on clinical grounds may be toxicity produced by the centrally acting antihypertensives such as clonidine (Chap. 60). Additionally, a myriad of traumatic, metabolic, and infectious etiologies may occur simultaneously and must always be considered and evaluated appropriately.

Naloxone Administration

The consequential effects of acute opioid poisoning are central nervous system and respiratory depression. Although early support of ventilation and ox-

ygenation is generally sufficient to prevent death, prolonged use of bag-valve mask ventilation and endotracheal intubation may be avoided by cautious administration of an opioid antagonist. Opioid antagonists, such as naloxone, competitively inhibit the binding of opioid agonists to the opioid receptors, allowing the patient to resume spontaneous respiration. Antidotes in Brief: Opioid Antagonists contains a more complete discussion of naloxone and other opioid antagonists.

The goal of naloxone therapy is not necessarily complete arousal; rather, the goal is reinstitution of adequate spontaneous ventilation. Because precipitation of withdrawal is potentially detrimental and often unpredictable, the lowest practical naloxone dose should be administered initially with rapid escalation as warranted by the clinical situation. Most patients respond to 0.05 mg of naloxone administered intravenously, although, because the onset may be slower than with larger doses, the requirement for ventilatory assistance may be slightly prolonged. Administration in this fashion will effectively avert endotracheal intubation and allow timely identification of patients with nonopioid causes for their clinical condition, yet diminish the risk of precipitation of acute opioid withdrawal. Subcutaneous administration may allow for smoother arousal than the high-dose intravenous route, but is unpredictable in onset and likely prolonged in offset. Prolonged effectiveness of naloxone by the subcutaneous route can be a considerable disadvantage if the therapeutic goal is exceeded and the withdrawal syndrome develops.

In the absence of a confirmatory history or diagnostic clinical findings, the cautious empiric administration of naloxone may be both diagnostic and therapeutic. Administration of naloxone to opioid-dependent patients may result in adverse effects; obviously, precipitation of an acute withdrawal syndrome should be anticipated. Additionally, emesis, a common feature of acute opioid withdrawal, may be particularly hazardous in patients who do not rapidly regain consciousness after naloxone administration (eg, concomitant ethanol or sedative-hypnotic exposure). This raises the risk for the pulmonary aspiration of vomitus if the airway is unprotected.

Identification of patients likely to respond to naloxone would conceivably reduce the unnecessary and potentially dangerous precipitation of withdrawal in opioid-dependent patients. A respiratory rate less than or equal to 12 breaths per minute in an unconscious patient presenting via emergency medical services (EMS) best predicts a response to naloxone. Regardless, relying on the respiratory rate to assess the need for ventilatory support or naloxone administration is not ideal because hypoventilation secondary to hypopnea may precede that caused by bradypnea.

The decision to discharge a patient who awakens appropriately following naloxone administration is based on practical considerations. Those patients manifesting only moderate signs of poisoning who remain normal for at least several hours following parenteral naloxone, and who have no other clinical concerns (eg, suicide risk) are likely safe to discharge.

THE OPIOIDS

The vast majority of opioid-poisoned patients follow predictable clinical courses that can be anticipated based on our understanding of opioid-receptor pharmacology. However, certain opioids taken in overdose may produce atypical manifestations. Consequently, careful clinical assessment and institution of empiric therapy is usually necessary to ensure proper management (Table 38–3).

TABLE 38–3. Classification, Potency, and Characteristics of Opioids

Agent (Representative Trade Name)	Type[a]	Analgesic Dose (mg) (Via Route, Equivalent to 10 mg Morphine SC[b])	Comments[a,c]
Buprenorphine (Buprenex, Subutex, Suboxone)	P/AA	0.4 IM	Analgesic only in opioid naive patients; may cause withdrawal if opioid dependent; opioid substitution therapy requires 6–16 mg/d; Suboxone contains naloxone to limit intravenous abuse
Codeine	Ag	120 PO	Analgesic and antitussive; often combined with acetaminophen; requires demethylation to morphine by CYP2D6 for analgesia
Dextromethorphan (Robitussin DM)	NEC	Nonanalgesic (10–30 PO)	Antitussive; widely abused by youth for psychotomimetic effects, which are similar to ketamine, via σ or NMDA receptor; may cause serotonin syndrome
Fentanyl (Sublimaze)	Ag	0.125 IM	Very short-acting (<1 h); transmucosal or transdermal use; poorly bioavailable enterally; fentanyl and congeners (eg, methylfentanyl) are often implicated as adulterants in epidemic "heroin" poisonings
Heroin, Diacetylmorphine, Diamorph	Ag	5 SC	Schedule I in the United States; requires conversion to morphine by carboxylesterase; more pure forms suitable for intranasal use; "chasing the dragon" is inhalation of heroin pyrolosate; body packing for smuggling is common
Hydrocodone (Vicodin, Hycodan)	Ag	10 PO	Widely abused
Hydromorphone (Dilaudid)	Ag	1.5 IM	
Meperidine, pethidine (Demerol)	Ag	75 SC/IM	More euphoric than other opioids; seizures due to metabolite accumulation (normeperidine); generally not used for acute pain control; sometimes for postoperative or chemotherapy related shivering; may cause serotonin syndrome

(continued)

TABLE 38–3. Classification, Potency, and Characteristics of Opioids *(continued)*

Agent (Representative Trade Name)	Type[a]	Analgesic Dose (mg) (Via Route, Equivalent to 10 mg Morphine SC[b])	Comments[a,c]
Methadone (Dolophine)	Ag	10 IM	Very long-acting (24 h); often need prolonged observation or naloxone infusion; QTc prolongation possible, even in therapeutic dosing
Morphine	Ag	10 SC/IM	Gold standard opioid
Nalmefene (Revex)	Ant	Nonanalgesic (0.1 IM)	Long-acting antagonist (4–6 h)
Naloxone (Narcan)	Ant	Nonanalgesic (0.1–0.4 IV/IM)	Short-acting antagonist (0.5 h)
Naltrexone (Trexan)	Ant	Nonanalgesic (50 PO)	Very-long-acting antagonist (24 h)
Oxycodone (Percocet, OxyContin)	Ag	10 PO	Often combined with acetaminophen (Percocet); OxyContin is sustained release (SR) preparation with relatively large amounts of oxycodone that is abused, particularly following disruption of SR matrix
Pentazocine (Talwin)	AA	50 SC	Psychotomimetic via σ receptor
Propoxyphene (Darvon)	Ag	65 PO	Seizures, dysrhythmias; combined with acetaminophen
Tramadol (Ultram)	Ag	50–100 PO	Seizures possible with therapeutic dosing and overdose; serotonergic effects are important therapeutically

[a]Agonist–antagonists, partial agonists, and antagonists may cause withdrawal in tolerant individuals.
[b]Typical dose (mg) for agents without analgesic effects is given in parentheses.
[c]Duration of therapeutic clinical effect 3–6 hours unless noted; likely to be exaggerated in overdose.
[d]Although approximately equipotent with methadone, LAAM is not used as an analgesic.
Ag=full agonist (μ_1, μ_2, κ); AA=agonist antagonist (κ agonist, μ antagonist); Ant=full antagonist (μ_1, μ_2, κ antagonist); P=partial agonist (μ_1, μ_2 agonist, κ antagonist); NEC=not easily classified.

Opioid Antagonists

Naloxone, nalmefene, and naltrexone are pure competitive opioid antagonists at the mu (μ), kappa (κ), and delta (δ) receptors. Naloxone is used to reverse respiratory depression for patients manifesting opioid toxicity. The parenteral dose should be titrated to maintain adequate airway reflexes and ventilation. Naltrexone is used orally for patients following opioid detoxification to maintain opioid abstinence and also as an adjunct to achieve ethanol abstinence. Nalmefene is a parenteral drug whose duration of action falls between naloxone and naltrexone.

PHARMACOLOGY

Naloxone, naltrexone, and nalmefene are pure competitive opioid antagonists at all opioid-receptor subtypes, preventing the binding of agonists, partial agonists, and mixed agonist–antagonists without producing any independent action. These antagonists are typically most potent at the μ receptor, often necessitating higher doses for effects at the κ and δ receptors. Naloxone, naltrexone, and nalmefene are similar in their antagonistic ability, but differ primarily in their pharmacokinetics, with both nalmefene and naltrexone having longer durations of action than naloxone. Naltrexone can be administered orally.

In the proper doses, pure opioid antagonists reverse all of the effects of endogenous and exogenous opioid agonists, except for those of buprenorphine, which has a very high affinity for and slow rate of dissociation from the μ receptor. Actions of opioid agonists that are not mediated by interaction with opioid receptors, such as direct mast-cell liberation of histamine or the sodium channel-blocking effects of propoxyphene, are not reversed. Opioid-induced seizures in animals tend to be antagonized by opioid antagonists, with the exception of those caused by meperidine and tramadol.

Extremely low doses of opioid antagonists (ie, 0.25 μg/kg/h of naloxone) enhance the analgesic potency of the opioid and attenuate or prevent the development of tolerance and dependence. It is hypothesized that these beneficial effects result from modulating the opposing excitatory effects of opioids.

PHARMACOKINETICS AND PHARMACODYNAMICS

Oral naloxone is poorly bioavailable because of extensive first-pass effect. Naloxone is well absorbed by most parenteral routes. The elimination half-life is 60–90 minutes in adults, and approximately 2–3 times longer in neonates. The duration of action of naloxone is approximately 20–90 minutes and depends on the dose of the agonist, the dose and route of administration of the naloxone, and the rate of elimination of the agonist and naloxone. The onset of action with the various routes of administration are as follows: intravenous 1–2 minutes; subcutaneous approximately 5.5 minutes; intralingual 30 seconds; intranasal 3.4 minutes; nebulization 5 minutes (when 2 mg is mixed with 3 mL of 0.9% NaCl solution); endotracheal within 60 seconds; and intramuscular no precise data available.

Naltrexone is rapidly absorbed, with peak plasma concentrations occurring at 1 hour and an oral bioavailability of 5–60%. The plasma elimination half-life is 10 hours, and the duration of effect is approximately 8–24 hours.

Nalmefene is a derivative of naltrexone, with an oral bioavailability of 40%. After oral administration, peak plasma concentrations are usually reached within 1–2 hours. Following oral administration, its half-life is 8–9 hours.

ADVERSE DRUG EFFECTS

Opioid antagonists prevent the actions of opioid agonists if administered as pretreatment, reverse the effects of endogenous and exogenous opioids, and unmask the manifestations of opioid withdrawal in opioid-dependent patients. Adverse effects excluding withdrawal and resedation are rare. Patients tolerant to opioid agonists exhibit opioid withdrawal reactions (yawning, lacrimation, diaphoresis, rhinorrhea, piloerection, mydriasis, vomiting, diarrhea, myalgias, mild elevations in heart rate and blood pressure, and insomnia) when exposed to opioid antagonists or agonist–antagonists such as pentazocine. An "overshoot" phenomenon is described where reversal leads to a transient increase in catecholamines, resulting in hyperventilation, tachycardia, and hypertension to higher levels than prior to baseline, with the potential for myocardial ischemia and acute lung injury.

If vomiting occurs because of withdrawal while the patient's airway is unprotected, aspiration pneumonitis may complicate the patient's recovery. Resedation is a function of the relative duration of action of the opioid antagonist and the opioid agonist. Acute lung injury, hypertension, and cardiac dysrhythmias are associated with naloxone administration, and may be causative in some situations. The contribution of naloxone is complicated by the fact that naloxone may be unmasking the acute lung injury previously induced by the opioid, but which is unrecognized because of the patient's respiratory depression. Although delirium is rarely reported, it may occur when naloxone is used to reverse patients tolerant to high doses of opioids or during rapid opioid detoxification.

Considering the large number of naloxone doses administered, naloxone has a remarkably safe profile, especially when used in low doses and titrated to effect.

USE FOR OPIOID AND ETHANOL ABSTINENCE

Opioid dependence is managed by detoxification and prolonged opioid abstinence, or substitution with methadone, buprenorphine, or naltrexone. Any pure opioid antagonist could be substituted, but naltrexone is chosen because of its oral absorption and long duration of action as compared to that of naloxone or nalmefene.

Naltrexone is also used as adjunctive therapy in ethanol dependence based on the theory that the endogenous opioid system modulates the intake of ethanol. Naltrexone reduces ethanol craving, the number of drinking days, and relapse rates.

DOSING

The final dose of the antagonist is dependent on the dose of the agonist and the relative binding affinity of the agonist and antagonist at the opioid receptors. The presence of an opioid with a greater affinity for the κ or δ receptor,

such as pentazocine or butorphanol, requires a larger-than-ordinary dose of antagonist to cause reversal. The duration of action of the antagonist depends on many drug and patient variables, including the dose and clearance of both antagonist and agonist.

A dose of naloxone of 0.4 mg IV reverses the respiratory-depressant effects of most opioids and is an appropriate starting dose in the non-opioid-dependent patient. However, this dose usually produces withdrawal in an opioid-tolerant patient. The goal is to reverse respiratory depression without inducing withdrawal. Consequently, 0.05 mg is a practical starting dose in most patients, increasing to 0.4 mg, then to 2 mg, and finally to 10 mg as needed. If there is no response to 10 mg, then an opioid is unlikely to be responsible for the respiratory depression.

Evaluation of the return of respiratory depression should be monitored continuously and resedation should be treated with either repeated doses of the antagonist or, if necessary, with another bolus followed by a continuous infusion.

An oral dose of 150 mg of naltrexone generally lasts 72 hours, which should be adequate as an antidote for the majority of patients. Naltrexone should never be administered to a patient who is opioid tolerant.

The initial intravenous dose of nalmefene is 0.1 mg in a 70-kg person in whom opioid dependency is suspected. If withdrawal does not ensue, 0.5 mg can be given, followed by 1 mg in 2–5 minutes as necessary. If intravenous access is unavailable, the intramuscular or subcutaneous route may be used, but the onset of action is delayed by 5–15 minutes after a 1-mg dose. For the reversal of postoperative opioid depression, a starting dose of 0.25 μg/kg is used, followed by incremental doses of 0.25 μg/kg every 2–5 minutes to the desired effect or to a total of 1 μg/kg. The experience with nalmefene is too limited to estimate an adequate observation time, although 24 hours seems prudent.

39 Dieting Agents and Regimens

Currently, medicinal weight-loss therapies are available as prescription medications (sibutramine, phentermine) and nonprescription dietary supplements (*Citrus aurantium*, chitosan, *Garcinia cambogia*). Natural weight-loss remedies have undergone a resurgence in use since passage of the Dietary Supplement Health and Education Act (known as DSHEA) of 1994 created a new category, separate from food and drugs, which includes vitamins, minerals, herbs, and amino acids, which are minimally regulated by the Food and Drug Administration (FDA). As a result, numerous botanicals and other substances are offered to consumers as weight-loss aids, some of which have no proven efficacy, and some with potentially serious toxicity.

Despite the disparate classes of dieting aids, they generally act through one or more of the following mechanisms: (a) appetite suppression, known as anorectics; (b) alteration of food absorption or elimination; or (c) increased energy expenditure (Table 39–1). Dieting aids that are anorectics are designed to decrease appetite and calorie intake. Anorectic agents may be serotonergic drugs (sibutramine) or sympathomimetics (amphetamines and derivatives), and have the potential to cause adverse stimulant effects and dependence. Certain agents, such as "starch blockers" and "fat blockers" (orlistat, chitosan), inhibit absorption of ingested nutrients. Dietary fiber pills act by absorbing large amounts of water and expanding in the stomach and intestinal tract to produce the satiety sensation of a large meal, and are causally linked to intestinal obstruction. Very-low-calorie diets, high-protein liquid supplements, and "dieter's teas" containing laxatives are associated with dehydration, severe electrolyte disturbances, and sudden cardiac death. Dinitrophenol and thyroid hormone have been used to increase basal energy expenditure, and are associated with cases of severe toxicity.

A number of weight-loss therapies were withdrawn or banned by the FDA because of serious adverse health effects (Table 39–2).

SYMPATHOMIMETICS

Sympathomimetic amines that act at α- and β-adrenergic receptors are clinically effective in promoting weight loss, but have numerous side effects that limit their clinical usefulness. The prototype sympathomimetic drug, amphetamine, was noted to cause weight loss soon after its introduction as a pharmaceutical for nasal congestion in the 1930s. The primary mechanism of action of the weight loss effects of sympathomimetic drugs is central nervous system stimulation resulting from increased release of norepinephrine and dopamine. The resulting effects include direct suppression of the appetite center in the hypothalamus and increased energy expenditure. Significant side effects, as well as abuse potential, severely limit the therapeutic use of this class of drugs.

TABLE 39–1. Approved Weight Loss Drugs and Dietary Supplements

Drug or Supplement[a]	Mechanism of Action	Regulatory Status	Adverse Effects/Contraindications[b]
	Sympathomimetics		
Diethylpropion (Tenuate) Mazindol (Mazanor, Sanorex) Phentermine (Fastin, Adipex)	Increased release of norepinephrine and dopamine	Schedule IV prescription drugs	Dry mouth, tremor, insomnia, headache, agitation, palpitations, hypertension, stroke, dysrhythmias Contraindications: MAOI use within 14 days, glaucoma, hyperthyroidism
Bitter orange extract (*Citrus aurantium*)	Contains synephrine increased thermogenesis and lipolysis(unproven)	Dietary supplement	Hypertension, cerebral ischemia, myocardial ischemia, prolonged QTc interval
Guarana	Contains caffeine, which may increase thermogenesis	Dietary supplement	Nausea, vomiting, insomnia, diuresis, anxiety, palpitations
	Serotonergics		
Sibutramine (Meridia)	Inhibits reuptake of serotonin and norepinephrine	Schedule IV prescription drug	Anxiety, dry mouth, insomnia, headache, hypertension, palpitations, dysmenorrhea Contraindications: same as sympathomimetics
	GI Agents		
Orlistat (Xenical)	Inhibits gastric and pancreatic lipases	Prescription drug	Abdominal pain, oily stool, fecal urgency or incontinence; fat-soluble vitamin loss Contraindications: cholestasis, chronic malabsorptive states
Chitosan	Insoluble marine fiber that binds dietary fat	Dietary supplement	Decreased absorption of fat-soluble vitamins Contraindications: shellfish allergy
	Fibers/Other Supplements		
Glucomannan	Expands in stomach to increase satiety	Dietary supplement	GI obstruction with tablet form Contraindications: abnormal GI anatomy
Garcinia cambogia	Increases fat oxidation (unproven)	Dietary supplement	None reported
Chromium picolinate	Improves blood glucose and lipids; produces fat loss (unproven)	Dietary supplement	Dermatitis, hepatitis, possibly mutagenic in high doses

[a]Trade names or Latin binomials are given in parentheses.
[b]All agents are contraindicated during pregnancy and lactation.

TABLE 39–2. Unapproved Weight Loss Drugs and Supplements

Drug or Supplement[a]	Mechanism of Action	Adverse Effects	Regulation Status DEA Schedule or Withdrawal Date
Amphetamine	Increased release of NE and dopamine	Sympathomimetic effects, psychosis, dependence	Schedule II
Benzphetamine (Didrex)	Increased release of NE and dopamine	Sympathomimetic effects, psychosis, dependence	Schedule III
Clenbuterol	β_2- and β_3-Adrenergic agonist activity	Tachycardia, headache, nausea, vomiting; may be prolonged	Not approved
Dexfenfluramine (Redux)	Promotes central serotonin release and inhibits its reuptake	Valvular heart disease, primary pulmonary hypertension	Withdrawn September 1997
Dieter's teas (senna, cascara, aloe, buckthorn)	Stimulant laxative herbs that promote colonic evacuation	Diarrhea, vomiting, nausea, abdominal cramps, electrolyte disorders, dependence	FDA required label warning—June 1995
Dinitrophenol	Alters metabolism by uncoupling oxidative phosphorylation	Hyperthermia, cataracts, hepatotoxicity, fatalities	Not approved
Ma-huang (*Ephedra sinica*)	Increased release of NE and dopamine	Sympathomimetic effects, psychosis	Banned by FDA—April 2004
Fenfluramine (Pondimin)	Increased release and decreased reuptake of serotonin	Valvular heart disease, primary pulmonary hypertension	Withdrawn September 1997
Guar gum (Cal-Ban 3000)	Hygroscopic polysaccharide swells in stomach, producing early satiety	Esophageal and small bowel obstruction, fatalities	Banned by FDA—July 1992
Lipokinetix (sodium usniate, norephedrine, 3,5-diiodothyronine, yohimbine, caffeine)	Unknown	Acute hepatitis	FDA warning—November 2001
Phendimetrazine (Adipost, Bontril)	Increased release of NE and dopamine	Sympathomimetic effects, psychosis	Schedule III
Phenylpropanolamine (Dexatrim, Acutrim)	α_1-Adrenergic agonist	Headache, hypertension, myocardial infarction, intracranial hemorrhage	Withdrawn November 2000

[a]Trade names are given in parentheses.
NE = norepinephrine.

Absence of polar hydroxyl groups from a sympathomimetic amine increases its lipophilicity. Consequently, unsubstituted or predominantly alkyl group-substituted compounds have greater central nervous system activity (eg amphetamine, ephedrine, phenylpropanolamine [PPA]). Mild cardiovascular and central nervous system (CNS) stimulant effects include headache, tremor, sweating, palpitations, and insomnia. More severe effects that can occur after overdose of sympathomimetic amines include anxiety, agitation, psychosis, seizures, palpitations, or chest pain. Cardiac ischemia, dysrhythmias, and stroke are reported. Life-threatening drug interactions with monoamine oxidase inhibitors may occur.

Hypertension is common following overdose, as well as occasionally following therapeutic use, and patients may present with confusion and altered mental status as a result of hypertensive encephalopathy. Reflex bradycardia after agents with predominantly α-adrenergic agonist effects may accompany the hypertension and provides a clue to the diagnosis. Children with unintentional ingestions may be at an especially high risk for hypertensive episodes as a consequence of the relatively significant dose per kilogram of body weight. Other manifestations include chest pain, palpitations, tachycardia, syncope, hypertension, mania, psychoses, convulsions, and coronary vasospasm.

Clinically significant hypertension should be treated aggressively, either with phentolamine, a rapidly acting α-adrenergic antagonist, or nitroprusside. Analogous to the management of cocaine toxicity, β-adrenergic antagonists should be avoided because the resultant unopposed α-adrenergic agonist effects may lead to greater vasoconstriction and increased hypertension. Agitation, tachycardia, and seizures should be treated with benzodiazepines.

Phenylpropanolamine

Phenylpropanolamine, another sympathomimetic amine, was available until 2000 as a nonprescription diet aid (eg, Dexatrim, Acutrim) when its use was linked to an increased risk of hemorrhagic stroke in women. It is both direct acting, via stimulation of α-adrenergic receptors, and indirect acting, through release of norepinephrine. Both of these actions tend to cause a net increase in blood pressure when given in high doses.

Ephedrine

Ephedra (*Ephedra sinica*), or Ma huang in Chinese herbal nomenclature, is a plant that contains 6 sympathomimetic amines, known collectively as ephedra alkaloids. FDA banned ephedra-containing products in April 2004 because of a large number of reported cases of serious cardiovascular toxicity associated with use of these products. In 2005, this ban was partially overturned by the courts, but ultimately upheld. Regardless, ephedra can still be obtained from practitioners of alternative medicine as a traditional Chinese herbal medicine for short-term treatment of wheezing and nasal congestion associated with asthma, allergies, and colds or flu. Since ephedra was banned, herbal weight-loss supplements have been reformulated. Many now contain an extract of bitter orange (*Citrus aurantium*), a natural source of the sympathomimetic amine, synephrine, often in combination with caffeine, willow bark (containing salicylates), diuretics, and other constituents. The dried fruit peel of bitter orange, known in Chinese herbal medicine as Zhi shi, contains *p*-synephrine, another analog of amphetamine.

SEROTONERGICS

Drugs that affect central release and reuptake of serotonin are approved for a number of indications, including depression, anxiety, nicotine addiction, and premenstrual dysphoric syndrome. Although these drugs all reduce food intake to varying degrees, sibutramine (Meridia) is the only FDA-approved serotonergic specifically indicated for treating obesity. Sibutramine acts by blocking the reuptake of both serotonin and norepinephrine, but does not promote neuronal release of serotonin.

Sibutramine use is associated with hypertension, cardiac ischemia, and death. Because sibutramine raises heart rate and blood pressure, it should not be used in patients with poorly controlled hypertension, coronary artery disease, glaucoma, or previous stroke. Sibutramine taken in combination with monoamine oxidase inhibitors, or serotonin reuptake inhibitors, or any drug that affects serotonin release or reuptake, could induce serotonin syndrome, characterized by agitation, hyperthermia, autonomic instability, and myoclonus.

Serotonergics used in the past to treat obesity include dexfenfluramine (Redux), and fenfluramine (Pondimin), but these drugs have been withdrawn because of postmarketing reports of serious cardiac effects associated with their therapeutic use. A diet drug combination known familiarly as "Fen-Phen" from its 2-drug prescription regimen of fenfluramine and phentermine (an amphetamine derivative), was popular in the 1990s because of the presumed improved side-effect profile and efficacy achieved with lower doses of each drug. This drug combination was never approved by the FDA for treating obesity, and fenfluramine was withdrawn in 1997 when an unusual cardiac valvulopathy was described in 24 women taking Fen-Phen. Primary pulmonary hypertension also was described in association with fenfluramine and dexfenfluramine.

XENOBIOTICS THAT ALTER FOOD ABSORPTION, METABOLISM, AND ELIMINATION

Fat Absorption Blockers

Orlistat (Xenical) is a potent inhibitor of gastric and pancreatic lipase, thus reducing lipolysis and increasing fecal fat excretion. The drug is not systemically absorbed. It inhibits hydrolysis of dietary triglycerides, and reduces absorption of the products of lipolysis, monoglycerides, and free fatty acids. Adverse effects correlate with the amount of dietary fat consumption and include abdominal pain, oily stool, fecal incontinence, fecal urgency, flatus, and increased defecation. Because orlistat reduces absorption of fat-soluble food constituents, daily ingestion of a multivitamin supplement containing vitamins A, D, K, and β-carotene is advised to prevent resultant deficiency.

Chitosan is a weight-loss dietary supplement derived from exoskeletons of marine crustaceans that is thought to act similarly to orlistat by binding to dietary lipids in the gastrointestinal tract and reducing breakdown and absorption of fat.

Dietary Fibers

Guar gum, a hygroscopic polysaccharide, is derived from the bean of the *Cyamopsis psorabides* plant. It was marketed in pill or tablet form as Cal-Ban 3000 until it was banned by the FDA in 1992, because of its potential to cause

esophageal and small-bowel obstruction. Guar gum expands 10–20-fold in the stomach, forming a gelatinous mass that produces the sensation of satiety.

Glucomannan is a dietary fiber consisting of glucose and mannose, which is derived from konjac root, a traditional Japanese food. On contact with water, glucomannan swells to approximately 200 times its original dry volume, turning into a viscous liquid. Esophageal obstruction is a concern. Serious adverse effects are not described with encapsulated glucomannan presumably because slower dissolution allows for gastrointestinal transit prior to expansion.

Dinitrophenol

Dinitrophenol (DNP) increases metabolic work by uncoupling oxidative phosphorylation in the mitochondria by acting as an ionophore. Through this mechanism, the hydrogen ion gradient that allows adenosine triphosphate (ATP) synthesis is dissipated, preventing the proton motive force from creating high energy phosphate bonds (Chap. 13). Because the energy loss resulting from inefficient substrate utilization is dissipated as heat, elevated temperature and occasionally life-threatening hyperthermia can occur. Symptoms related to DNP toxicity include malaise, skin rash, headache, diaphoresis, thirst, and dyspnea. Severe toxic effects include hyperpyrexia, hepatotoxicity, agranulocytosis, respiratory failure, coma, and death. Delayed-onset cataract was a frequent and serious complication of DNP use.

Cathartic/Emetic Abuse

Dieter's teas that contain combinations of herbal laxatives, including senna and *Cascara sagrada,* can produce profound diarrhea, volume depletion, and hypokalemia, and are associated with cases of sudden death, presumably caused by cardiac dysrhythmias. Chronic laxative use can result in an atonic colon ("cathartic bowel"), and development of tolerance, with the subsequent need to increase dosing to achieve catharsis.

Chronic use of syrup of ipecac to induce emesis by patients with eating disorders such as bulimorexia leads to the development of cardiomyopathy, subsequent dysrhythmias, and death. Emetine, a component of syrup of ipecac, is the alkaloid responsible for the severe myopathy experienced by these patients. In 2003, an FDA advisory committee recommended that the nonprescription drug status of ipecac be rescinded because of its use by patients with bulimic disorders.

40 | Iron

HISTORY AND EPIDEMIOLOGY

Despite its long history of use, the first reports of iron toxicity only occurred in the mid-20th century. In the 1990s iron became the leading cause of poisoning deaths in children younger than 6 years of age. In 1997, the Food and Drug Administration (FDA) mandated the placement of warning labels on all iron salt-containing preparations regarding the dangers of pediatric iron poisoning. Other preventive initiatives instituted in 1997 included FDA-mandated warning labels, unit dosing (blister packs) of prescriptions containing more than 30 mg of elemental iron, and limiting the number of pills dispensed (ie, maximum 30-day supply). These efforts to prevent unintentional exposure dramatically decreased the incidence of morbidity and mortality associated with iron poisoning. Unfortunately, the blister packaging requirement was rescinded by the FDA in 2003. Two newer nonionic forms—carbonyl iron and iron polysaccharide—both appear less toxic than iron salts.

PHARMACOLOGY AND TOXICOKINETICS

Iron is critical to organ function because it is able to accept and donate electrons easily as it shifts from ferric (Fe^{3+}) to ferrous (Fe^{2+}) states. This reduction-oxidation (redox) interchange gives iron an essential role in multiple protein and enzyme complexes, including cytochromes, myoglobin, and hemoglobin. Insufficient iron results in anemia, whereas excess total-body iron results in hemochromatosis.

Iron stores are regulated by controlling its absorption from the gastrointestinal tract. In iron deficiency, iron uptake increases from a normal of 10–35% to as much as 80–95%. Following uptake, iron is either stored as ferritin and lost when the cell is sloughed, or released to transferrin, a serum iron-binding protein. In therapeutic doses, some of these processes become saturated and absorption is limited. However, in overdose the oxidative and corrosive effects of iron on gastrointestinal mucosal cells lead to dysfunction of this regulatory balance and increase passive absorption of iron.

Iron supplements are available as the iron salts ferrous gluconate, ferrous sulfate, and ferrous fumarate, and as the nonionic preparations carbonyl iron and polysaccharide iron. Additional sources of significant quantities of iron are vitamin preparations, especially prenatal vitamins. Toxicity is based on the amount of elemental iron in each preparation (Table 40–1). Iron polysaccharide and carbonyl iron appear to be safer formulations than iron salts despite high elemental iron content. Carbonyl iron is a form of elemental iron that is highly bioavailable. Toxicity is limited in overdose because carbonyl iron must be solubilized to be absorbed. The slow oxidation of carbonyl iron to ferrous (Fe^{2+}) ion in stomach acid serves as a rate-limiting step. In rats, carbonyl iron has an LD_{50} (median lethal dose for 50% of test subjects) of 50 g/kg compared with an LD_{50} of 1.1 g/kg of ferrous sulfate. Iron polysaccharide contains approximately 46% elemental iron by weight. The estimated LD_{50} in rats is more than 5 g/kg.

TABLE 40–1. Common Iron Formulations and Their Elemental Iron Contents

Iron Formulation	Elemental Iron
Ionic	
Ferrous chloride	28%
Ferrous fumarate	33%
Ferrous gluconate	12%
Ferrous lactate	19%
Ferrous sulfate	20%
Nonionic	
Carbonyl iron	98%[a]
Iron polysaccharide	46%[a]

[a]Although these nonionic iron formulations contain higher elemental iron content than ionic formulations, carbonyl iron and iron polysaccharide have better therapeutic-to-toxic ratios.

PATHOPHYSIOLOGY

The participation of iron in redox reactions such as the Fenton reaction and Haber-Weiss cycle causes oxidative stress. Generation of reactive oxygen species oxidize membrane-bound lipids and result in the loss of cellular integrity with subsequent tissue injury. Oxidative damage to the GI epithelium enhances iron entry into the systemic circulation. Iron ions are rapidly bound to circulating binding proteins, particularly transferrin. Once transferrin is saturated with iron, "free" iron (iron not bound safely to a transport protein) is widely distributed to the various organ systems where it promotes damage. Iron ions disrupt mitochondrial oxidative phosphorylation leading to a metabolic acidosis. In addition, as iron is absorbed from the gastrointestinal tract, ferrous iron (Fe^{2+}) is converted to ferric iron (Fe^{3+}). Ferric iron ions exceed the binding capacity of plasma, leading to formation of ferric hydroxide and production of three protons ($Fe^{3+} + 3H_2O \rightarrow Fe[OH]_3 + 3H^+$).

In animals, decreased cardiac output contributes to hemodynamic shock. Although significant volume loss is contributory, iron also has a direct negative inotropic effect on the myocardium. Free iron inhibits thrombin and the effect of thrombin on fibrinogen, with coagulopathy occurring independently of hepatotoxicity.

CLINICAL MANIFESTATIONS

Toxic gastrointestinal effects of iron poisoning occur at doses of 10–20 mg/kg elemental iron (Table 40–1). Above 50 mg/kg acidosis and hemodynamic instability should be expected. Doses greater than 100 mg/kg should be considered potentially life-threatening.

Although 5 stages of iron toxicity are described, a clinical stage should never be assigned based on the number of hours postingestion, as patients do not necessarily follow the same temporal course through these stages.

The first stage of iron toxicity is characterized by nausea, vomiting, abdominal pain, and diarrhea. The "local" toxic effects of iron predominate, and subsequent salt and water depletion contribute to the condition of the iron-poisoned patient. Intestinal ulceration, edema, transmural inflammation, and, in some extreme cases, small-bowel infarction and necrosis may occur. Hematemesis, melena, or hematochezia may cause hemodynamic instability. Gastrointestinal symptoms always follow significant overdose, and, con-

versely, the absence of vomiting in the first 6 hours following ingestion essentially excludes serious iron toxicity.

The "latent" or "second stage" of iron poisoning commonly refers to the period 6–24 hours following the resolution of gastrointestinal symptoms and before overt systemic toxicity develops. This second stage is not a true quiescent phase, as during this phase there is ongoing cellular toxicity. Gastrointestinal complaints resolve, but patients in the latent phase generally have lethargy, tachycardia, and metabolic acidosis.

Patients may progress to the third or shock stage of poisoning as early as the first few hours after a massive ingestion or 12–24 hours after a more moderate ingestion. The etiology of shock may be multifactorial, resulting from hypovolemia, vasodilation, and poor cardiac output. Coagulopathy may worsen bleeding and hypovolemia. Systemic toxicity produces CNS effects with lethargy, hyperventilation, seizures, or coma.

The fourth stage of iron poisoning is characterized by hepatic failure, which may occur 2–3 days following the ingestion. The hepatotoxicity is directly attributed to uptake of iron by the reticuloendothelial system in the liver, where it causes oxidative damage.

The fifth stage of iron toxicity rarely occurs. Gastric outlet obstruction, secondary to strictures and scarring from the initial gastrointestinal injury, can develop 2–8 weeks following ingestion.

DIAGNOSTIC TESTING

Radiography

Finding radiopaque pills on an abdominal radiograph is most useful as a guide for evaluating the success of gastrointestinal decontamination (see Figure 6–1). However, the absence of the radiographic evidence of pills is not a reliable indicator to exclude potential toxicity. Liquid iron formulations and chewable iron tablets are typically not radiopaque. Because adult iron preparations have a higher elemental iron content and do not readily disperse, they tend to be more consistently radiopaque.

Laboratory

A high anion gap metabolic acidosis that is primarily lactate is common in serious iron poisonings. Anemia may result from gastrointestinal blood loss, but may not be evident initially because of hemoconcentration secondary to plasma volume loss. Although frequently discussed, the elevated white blood cell count and glucose concentration actually have very little predictive value and decisions based on these values can be erroneous.

Although iron poisoning remains a clinical diagnosis, serum iron concentrations can be used effectively to gauge toxicity and the success of treatment. Peak serum iron concentrations occur 4–6 hours postingestion. Serum iron concentrations greater than 300 μg/dL are generally consistent with gastrointestinal symptoms. Serum iron concentrations between 300 and 500 μg/dL usually correlate with significant gastrointestinal toxicity and modest systemic toxicity. Concentrations between 500 and 1000 μg/dL are associated with pronounced systemic toxicity and shock, and concentrations greater than 1000 μg/dL are associated with significant morbidity and mortality. Lower concentrations cannot be used to exclude the possibility of serious toxicity, as a single value may not represent a peak concentration. Total iron-

binding capacity (TIBC) is not valuable for comparison to serum iron concentration, as TIBC factitiously increases as a result of iron poisoning and the method of laboratory determination.

MANAGEMENT

Initial Approach

Figure 40–1 summarizes the overall approach to iron poisoning. As in the case of any serious ingestion, initial stabilization must include supplemental oxygen, an assessment of airway, and establishment of intravenous access. Intravenous volume repletion should begin while considering orogastric lavage and whole-bowel irrigation. Early endotracheal intubation may facilitate safe gastrointestinal decontamination in patients with altered mental status or hemodynamic instability. An abdominal radiograph may be used to estimate the iron burden in the gastrointestinal tract and to gauge response to decontamination measures, given the discussion above. Laboratory values, including chemistries, hemoglobin, iron concentration, coagulation, and hepatic profiles, are necessary in the sickest patients. An arterial blood gas or venous blood gas, and stat electrolytes will rapidly detect a metabolic acidosis. Patients who are well appearing, or who have had only 1–2 brief episodes of vomiting, may be observed pending discharge or can have a serum iron concentration measured.

Limiting Absorption

Iron is not well adsorbed to activated charcoal. Because vomiting is a prominent early symptom for those with significant toxicity, little benefit is expected from induced emesis and this technique is no longer recommended. Orogastric lavage is more effective, but its effectiveness can be limited because of the large size and poor solubility of most iron tablets, their ability to form adherent masses, and their movement into the bowel. There are no data to support the use of oral deferoxamine, bicarbonate, phosphosoda, or magnesium to reduce absorption. If multiple radiopaque pills are visible in the stomach, lavage can be considered. When iron tablets have moved past the pylorus, whole-bowel irrigation (WBI) is preferred (see Antidotes in Brief: Whole-Bowel Irrigation). For patients with life-threatening toxicity and persistent iron in the gastrointestinal tract despite orogastric lavage and WBI, upper endoscopy or gastrotomy with surgical removal of iron tablets may both be necessary and lifesaving.

Deferoxamine

Intravenous administration of deferoxamine should be considered in all iron-poisoned patients with any of the following findings: metabolic acidosis, repetitive vomiting, toxic appearance, lethargy, hypotension, or signs of shock. Deferoxamine administration should also be considered in any patient with serum iron concentrations greater than 500 μg/dL. In patients manifesting serious signs and symptoms of iron poisoning, deferoxamine should be initiated as an intravenous infusion, starting slowly and gradually increasing to a dose of 15 mg/kg/h. Intramuscular administration of deferoxamine, although once a popular method of therapy and part of the "deferoxamine challenge" test, is no longer recommended.

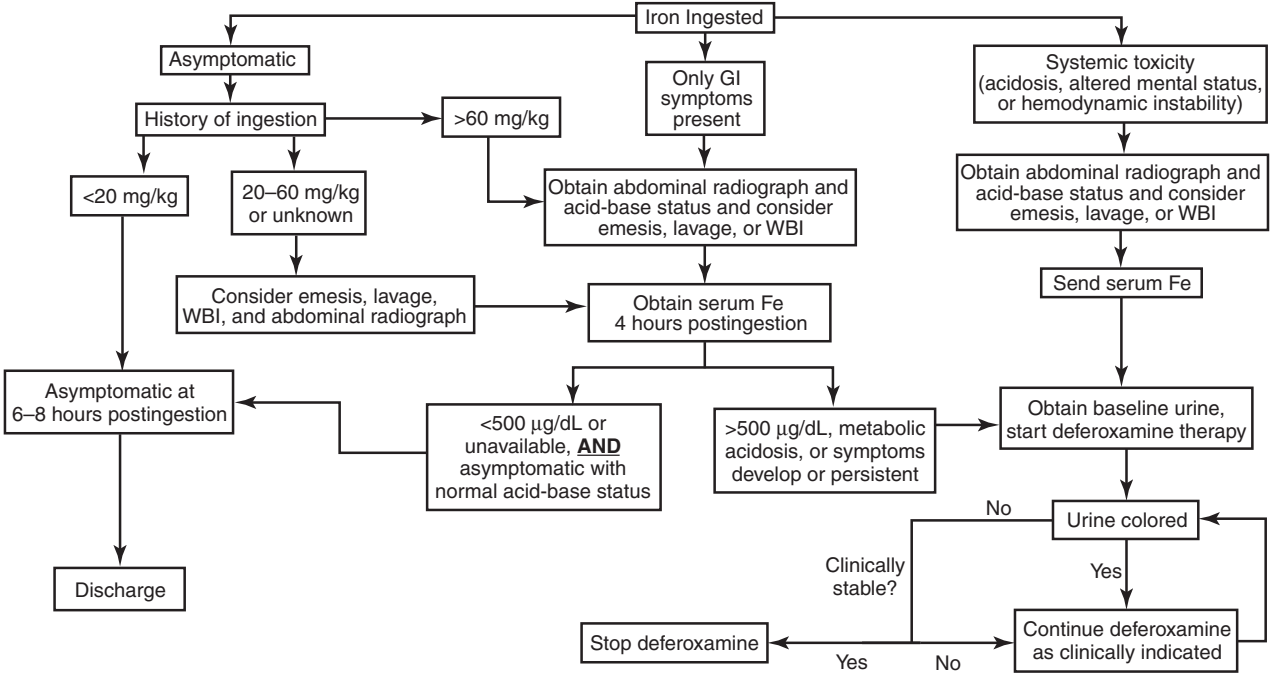

FIG. 40–1. Algorithm for decision analysis following iron ingestion.

Because of concern for possible deferoxamine toxicity, clinicians have attempted to define the earliest clear end points for deferoxamine therapy. Most authors agree that deferoxamine therapy should be discontinued when the patient appears clinically well, the anion gap acidosis has resolved, and there is no further urine color change. In patients with persistent signs and symptoms of serious toxicity following 24 hours of intravenous deferoxamine, continuing therapy should be undertaken cautiously and perhaps at a lower dose if at all because of the risk of ALI (see Antidotes in Brief: Deferoxamine).

Special Situation: Pregnant Patients

The frequent diagnosis of iron-deficiency anemia during pregnancy is associated with access to iron preparations with resultant serious, and even fatal, iron ingestions in pregnant women. Neither iron nor deferoxamine is transferred to the fetus in appreciable quantities. Fetal demise presumably results from maternal iron toxicity and not from direct iron toxicity to the fetus. Consequently, deferoxamine should be used to treat serious maternal iron poisoning and never withheld because of unfounded concern for fetal exposure to deferoxamine.

Alternative Therapies

One other treatment modality used experimentally for iron intoxication is continuous arteriovenous hemofiltration (CAVH). In an animal model, increased elimination of ferrioxamine was demonstrated in the ultrafiltrate when increasing doses of deferoxamine were infused into the arterial side of the system. This technique is not described in iron-poisoned humans. In toddlers with severe poisoning, exchange transfusion may help to physically remove free iron from the blood while replacing it with normal blood. However, because iron-poisoned patients tend to have hemodynamic instability, removing blood volume may not be well tolerated. The decision to use these alternative therapies should be based on a risk-to-benefit analysis.

Deferoxamine

CHEMISTRY

Ferrioxamine is a brownish-red compound containing trivalent iron (ie, ferric iron [Fe^{3+}]) isolated from the organism *Streptomyces pilosus*. Deferoxamine (desferrioxamine B) is the colorless compound that results when iron is removed from ferrioxamine B. One mole of deferoxamine (DFO) binds 1 mole of Fe^{3+}; therefore 100 mg of DFO as the mesylate salt can bind 8.5 mg of Fe^{3+}. Because DFO has a far greater affinity constant for iron (10^{31}) than for zinc, copper, nickel, magnesium, or calcium (10^{2}–10^{14}) at physiologic pH, it complexes almost exclusively with iron.

MECHANISM OF ACTION

DFO binds Fe^{3+} at three N–OH sites, forming an octahedral iron complex. The resultant ferrioxamine is very stable. Deferoxamine appears to benefit iron poisoned patients by chelating free iron (nontransferrin bound plasma iron) and iron in transit between transferrin and ferritin (chelatable labile iron pool), while not directly affecting the iron of hemoglobin, hemosiderin, or ferritin. Deferoxamine also binds "free iron" found in the plasma after transferrin is saturated. Additionally, deferoxamine chelates and inactivates cytoplasmic and mitochondrial iron, preventing disruption of mitochondrial function and injury.

PHARMACOKINETICS

The volume of distribution of DFO ranges from 0.6–1.33 L/kg, with an initial distribution half-life of 5–10 minutes and a terminal elimination half-life of approximately 6 hours in healthy patients. Unmetabolized DFO undergoes glomerular filtration and tubular secretion. In comparison, ferrioxamine has a smaller volume of distribution than DFO, which implies that DFO has a more extensive tissue distribution. Ferrioxamine is entirely eliminated by the kidney within 5 hours, through glomerular filtration and partial reabsorption.

ANIMAL STUDIES

Studies of iron poisoning in a variety of animal models show dramatic improvement in survival rates after DFO is administered. In fact, mortality rates directly correlate with the delay to DFO administration. However, dogs given iron-DFO complex orally had a 40–100% mortality, suggesting that oral DFO also may increase lethality.

EARLY HUMAN USE AND HISTORY OF DOSING RECOMMENDATIONS

In an early case series, 1 g of DFO was administered intravenously at a maximum of 15 mg/kg/h every 4–12 hours for patients in shock or who were severely ill. Of the 28 patients who developed coma, shock, or both, only 3 died, 1 of whom received late treatment with DFO.

URINARY COLOR CHANGE

In an attempt to further define the role of DFO, investigators studied urinary samples. A red or orange-brown color of the urine following DFO was found

to be indicative of 10–30 mg of urinary iron excretion per 24 hours. Currently, most data suggest that following DFO administration, the absence of a urine color change indicates that very little ferrioxamine is being excreted renally. However, unless a baseline urine is obtained prior to DFO administration, post-DFO administration comparisons of urine color are unreliable. No relationship between urinary iron excretion, clinical iron toxicity, and the effectiveness of DFO has been established.

PARENTERAL ADMINISTRATION

Prior to 1976, IM DFO was the preferred route of administration and IV DFO was reserved for patients in shock. However, when studied, IV DFO was found to significantly enhance urinary iron elimination. Currently, the IV route is preferred in all patients.

DURATION OF DOSING

Optimum duration of DFO administration is unknown. In canine models, serum iron concentrations peak within 3–5 hours and then fall quickly as iron is transported out of the blood into the tissues. In one human study, patients with initial iron levels of about 500 μg/dL fell to approximately 100 μg/dL within 12 hours. Other reports suggest that by 24 hours most of the easily accessible iron is distributed out of the blood compartment. Given that prolonged DFO is associated with toxicity, treatment for more than 24 hours is not routinely recommended.

ADVERSE EFFECTS

When administered to patients with acute iron overdose, DFO is associated with rate-related hypotension, delayed onset, and pulmonary toxicity. When administered to patients with chronic iron overload, DFO is associated with auditory, ocular, and pulmonary toxicity and infection. The mechanism for the rate-related hypotension is not fully understood, although histamine release is implicated. Intravascular volume depletion caused by iron toxicity also contributes to the hypotension. No experiment has ever determined a maximum safe rate of administration of DFO. The current recommendation for intravenous infusion of DFO is not to exceed 15 mg/kg/h.

Acute lung injury (ALI) occurs in patients with acute iron overdoses given IV DFO (15 mg/kg/h) therapy for longer than 24 hours. Usually there was a return to normal iron concentrations in these patients after 24 hours, and the rationale for continued administration of DFO was not reported.

Deferoxamine therapy may lead to infection with a number of unusual organisms, including *Yersinia enterocolitica*, *Zygomycetes*, and *Aeromonas hydrophilia*. The virulence of these organisms is facilitated when the DFO-iron complex acts as a siderophore for their growth.

Ocular toxicity characterized by decreased visual acuity, night blindness, color blindness, and retinal pigmentary abnormalities has occurred in patients who received continuous IV DFO for thalassemia and other nonacute iron- and aluminum-excess conditions. Ototoxicity documented by abnormal audiograms indicating partial or total deafness is also reported. However, neither ocular toxicity nor ototoxicity has been reported following the limited exposure associated with therapy for acute iron overdose.

USE IN PREGNANCY

Serious iron toxicity with organ involvement is associated with spontaneous abortion, preterm delivery, and maternal death. There is no evidence that deferoxamine is teratogenic. Neither iron nor deferoxamine appears to cross the ovine placenta. A review of 40 pregnant patients with thalassemia treated extensively with DFO found no evidence of teratogenicity. Therefore, deferoxamine should be administered to pregnant women with acute iron overdose for the same indications as for nonpregnant women.

USE IN ALUMINUM TOXICITY

Patients with renal insufficiency are at high risk for aluminum (Al) toxicity. Other etiologies of Al toxicity include bladder irrigation with alum and extensive use of Al-containing antacids. DFO binds Al to form aluminoxamine, which is excreted renally. In patients with renal insufficiency, hemodialysis (especially with a high flux membrane) is effective in removing the aluminoxamine. The dosing of DFO should be tailored to the patient's serum Al concentrations, symptomatology, and response. Doses of DFO of 15 mg/kg/day infused over 1 hour at 6–8 hours before hemodialysis have maximized aluminoxamine removal.

INDICATIONS AND DOSING

The indications and dosage schedules for DFO administration are largely empiric and the duration of therapy should probably be limited to 24 hours to maximize effectiveness while minimizing the risk of pulmonary toxicity. Typically, an intravenous infusion is increased as tolerated to a maximal rate of 15 mg/kg/h, but this recommendation remains to be validated experimentally. Although patients with mild toxicity may be treated with IM injections of DFO at 90 mg/kg (maximum: 1 g in children, 2 g in adults), this volume of antidote is quite painful and must be given in multiple injections in children. As a result, few clinicians administer DFO IM and most prefer the IV route. The total daily parenteral dose is limited by the infusion rate in children (if the manufacturer's recommendations are adhered to). In adults, conservative recommendations limit the dose to 6–8 g/day, although doses as high as 16 g/day have been administered without incident.

AVAILABILITY

Deferoxamine mesylate (Desferal) is available in vials containing 500 mg or 2 g of sterile, lyophilized powder. Addition of 5 mL or 20 mL of sterile water for injection to either the 500-mg or the 2-g vials, respectively, results in a solution of 100 mg/mL that is isotonic. The resulting solution can be further diluted with 0.9% NaCl solution, dextrose in water, or lactated Ringer solution for intravenous administration. For IM administration, a smaller volume of solution is preferred, and 2 mL or 8 mL of sterile water for injection can be added to the 500-mg or 2-g vials, respectively.

41 Vitamins

A vitamin is a substance that is present in small amounts in natural foods, is necessary for normal metabolism, and the lack of it in one's diet causes a deficiency disease. Millions of people in United States regularly ingest quantities of vitamins in great excess of the recommended dietary allowances (RDA) (Table 41–1). Some of these vitamins are associated with significant adverse effects when ingested in very large doses.

Vitamins can be divided into two general classes. Most of the vitamins in the water-soluble class have minimal toxicity because they are stored in the body to only a limited extent. Thiamine, riboflavin, cyanocobalamin (vitamin B_{12}), pantothenic acid, folic acid, and biotin are not reported to cause any toxicity following oral ingestion in excessive amounts. Ascorbic acid (vitamin C), nicotinic acid, and pyridoxine (vitamin B_6) are associated with toxicity syndromes. The fat-soluble vitamins can bioaccumulate to massive degrees. As a result, the potential for toxicity greatly exceeds that of the water-soluble group. Vitamins A, D, and E are all associated with toxicity in the setting of very large overdoses.

VITAMIN A

The term *vitamin A*, classically used to refer to the compound retinol, is now used to describe other naturally occurring derivatives of retinol as well. Deficiency results in nyctalopia, decreased vision in dim lighting, more commonly known as night blindness. Vitamin A activity is expressed in retinol equivalents (RE). One RE corresponds to 1 μg of retinol or 3.3 international units (IU) of vitamin A activity as retinol. Vitamin A, in the form of 11-*cis*-retinol, plays a critical role in the function of the retina.

Hypervitaminosis A can occur in people who ingest large doses of vitamin A in their daily diets. The tolerable upper intake level for adults is 3000 μg/d (9900 IU/d).

Although overingestion of certain foods such as polar bear liver has the ability to produce vitamin A toxicity, the majority of cases result from vitamin supplements.

Pharmacology and Toxicokinetics

The absorption of vitamin A in the small intestine is nearly complete. Approximately 90% of the body's total vitamin A content is stored in the liver as retinyl esters. Vitamin A is released into the plasma for delivery to other tissues as needed. A normal plasma retinol concentration is about 30–70 μg/dL. Excessive intake of vitamin A is not initially reflected as elevated blood concentrations. This is because vitamin A is soluble in fat but not in water. Instead, hepatic accumulation is increased. This storage system allows for cumulative toxic effects. Although there is no relationship between the magnitude of liver stores and blood concentrations of vitamin A, in chronic hypervitaminosis A, serum concentrations are generally greater than 95 μg/dL. Vitamin A has a half-life of 286 days in the blood.

TABLE 41–1. Recommended Dietary Daily Allowances/Adequate Daily Intakes

Age (y)	Vitamin A (μg RE/IU)	Vitamin D (μg/IU)	Vitamin E (mg α-TE/IU)	Vitamin C (mg)	Vitamin B_6 (mg)	Niacin (mg NE)
Infants						
0.0–0.5	400/1300	5/200	4/4	40	0.1	2
0.5–1.0	500/1700	5/200	5/5	50	0.3	4
Children						
1–3	300/990	5/200	6/6	15	0.5	6
4–8	400/1300	5/200	7/7	25	0.6	8
Males						
9–13	600/2000	5/200	11/11	45	1.0	12
14–18	900/3000	5/200	15/15	75	1.3	16
19–49	900/3000	5/200	15/15	90	1.3	16
50–70	900/3000	10/400	15/15	90	1.7	16
>70	900/3000	15/600	15/15	90	1.7	16
Females						
9–13	600/2000	5/200	11/11	45	1.0	12
14–18	700/2300	5/200	15/15	65	1.2	14
19–49	700/2300	5/200	15/15	75	1.3	14
50–70	700/2300	10/400	15/15	75	1.5	14
>70	700/2300	15/600	15/15	75	1.5	14

Pregnant						
≤18	750/2500	5/200	15/15	80	1.9	18
19–50	770/2500	5/200	15/15	85	1.9	18
Lactating						
≤18	1200/4000	5/200	19/19	115	2.0	17
19–50	1300/4300	5/200	19/19	120	2.0	17

RE, retinol equivalents; NE, niacin equivalents; TE, tocopherol equivalents.
Adapted from Food and Nutrition Information Center homepage. http://www.nal.usda.gov/fnic/etext/000105.html. Accessed April 27, 2005.

Clinical toxicity correlates well with total-body vitamin A content, which is a function of both dosage and duration of administration. The minimal dose required to produce toxicity in humans has not been established. Hepatoxicity may occur in humans following an acute ingestion of a massive dose of vitamin A (greater than 600,000 IU). Hypervitaminosis A occurs more frequently secondary to chronic ingestions of vitamin A. Hepatotoxicity typically requires ingestions of at least 50,000–100,000 IU of vitamin A per day for months or years.

Pathophysiology

Ninety percent of hepatic stores of vitamin A are located in the Ito, or fat-storing, cells. Ito cells undergo hypertrophy and hyperplasia as vitamin A storage is increased. This results in transdifferentiation of the Ito cell into a myofibroblastlike cell that secretes a variety of extracellular matrix components, leading to obstruction to sinusoidal blood flow and noncirrhotic portal hypertension. Continued ingestion of vitamin A may lead to cirrhosis.

Vitamin A toxicity is associated with idiopathic intracranial hypertension (IIH). Although vitamin A's role in the development of IIH is not definitively understood, serum concentrations of vitamin A are significantly higher in patients with IIH than in healthy controls.

Clinical Manifestations

Hypervitaminosis A affects the skin, hair, bones, liver, and brain. The most common skin manifestations include xerosis, associated with pruritus and erythema, skin hyperfragility, and desquamation. Toxicity may also cause hair thinning; shiny-appearing, brittle, or soft nails; dry mucous membranes with chapped lips and xerosis of nasal mucosa, which is associated with nasal bleeding. Epidemiologic studies are consistent with bone loss and a resulting increase in fracture risk, as well as skeletal hyperostoses, extra-spinal tendon and ligament calcifications, soft-tissue ossification, cortical thickening of bone shafts, periosteal thickening, and bone demineralization.

The degree of hepatotoxicity correlates with the dose of vitamin A and chronicity of use, and is manifested by elevations in bilirubin, aminotransferases, and alkaline phosphatase.

Isotretinoin is effective in the management of acne. However, its use is associated with teratogenicity. It is thought to interfere with cranial-neural-crest cells, which contribute to the development of both the ear and the conotruncal area of the heart, and may cause malformed or absent external ears or auditory canals and conotruncal heart defects.

Treatment with tretinoin (all-*trans*-retinoic acid), followed by anthracycline and cytarabine, improves the complete remission rate and reduces the incidence of relapse in cases of acute promyelocytic leukemia. Retinoic acid syndrome occurs in up to 25% of patients who receive tretinoin without prophylactic measures. The syndrome is characterized by dyspnea, pulmonary effusions and infiltrates, fever, weight gain, renal failure, pericardial effusions, and hypotension. Elevated leukocyte counts at diagnosis or rapidly increasing counts during tretinoin treatment predict the development of retinoic acid syndrome. Dexamethasone decreases the incidence of this syndrome to approximately 15% and its mortality to 1%.

Diagnostic Testing

Although an elevated serum vitamin A concentration can be determined, hepatotoxicity can occur prior to an elevation in the serum concentration. The

diagnosis of vitamin A hepatotoxicity is supported by histologic evidence of Ito cell hyperplasia with fluorescent vacuoles on liver biopsy.

Treatment

Management of an acute, large overdose should include a dose of activated charcoal. While most signs and symptoms of hypervitaminosis A resolve within 1 week with discontinuation of vitamin A and supportive care, papilledema and skeletal abnormalities may persist for several months. Visual impairment secondary to optic atrophy may be a permanent sequela of vitamin A toxicity. Hypercalcemia should be treated with intravenous fluids, loop diuretics, and 20 mg/d of prednisone. Bisphosphonates may be beneficial in refractory cases.

Idiopathic intracranial hypertension may require a more aggressive therapy, one similar to that for other causes of increased intracranial pressure (ICP). Depending on the severity of the syndrome, patients may require dexamethasone, acetazolamide, furosemide, and/or mannitol. Patients with extremely high ICP may also benefit from daily lumbar punctures with cerebrospinal fluid (CSF) drainage.

VITAMIN D

History and Epidemiology

Vitamin D is the name given to both cholecalciferol (vitamin D_2) and ergocalciferol (vitamin D_3). In humans, both forms of vitamin D have the same biologic potency. Vitamin D is used for the prophylaxis and treatment of rickets, osteomalacia, osteoporosis, hypoparathyroidism, and psoriasis.

Pharmacology

Vitamin D itself is not biologically active and must be extensively metabolized to an active form. Vitamin D_3 is synthesized in the skin from 7-dehydrocholesterol (provitamin D_3) in a reaction that is catalyzed by ultraviolet B irradiation. Vitamin D_3 is then bound to vitamin D-binding protein and enters the circulation. In the endoplasmic reticulum of the liver, vitamin D_3 is metabolized to 25-hydroxyvitamin D [25(OH)D] by vitamin D-25-hydroxylase. Once formed, 25(OH)D is again bound to vitamin D-binding protein and transported to the proximal convoluted tubule in the kidney for hydroxylation to 1,25-dihydroxy vitamin D [$1,25(OH)_2D$] or calcitriol by 25(OH)D-1α-hydroxylase. Once formed, $1,25(OH)_2D$ is secreted back into circulation, bound to vitamin D-binding protein, and delivered to target cells where it binds to receptors.

The primary role of vitamin D is to regulate calcium homeostasis via interactions with the intestines and bones. In the intestines, calcitriol increases the production of calcium-binding proteins and plasma membrane calcium pump proteins, thereby increasing calcium absorption through the duodenum. In the bone, calcitriol stimulates osteoclastic precursors to differentiate into mature osteoclasts. Mature osteoclasts, together with parathyroid hormone (PTH), lead to mobilization of calcium stores from bone, thereby raising serum concentrations of calcium.

Pathophysiology

The hallmark of vitamin D toxicity is hypercalcemia. Variation exists in the literature regarding the toxic dose of vitamin D, with little scientific data for

corroboration. The current "no observed adverse effect level" was conservatively set at 50 μg (2000 IU) per day. However, this did not take into account data showing that doses as high as 110 μg (4400 IU) per day and 2500 μg (100,000 IU) for 4 days did not result in adverse effects. Case reports describe toxicity in the setting of vitamin D intake of 50,000–150,000 IU, daily for prolonged periods of time.

Clinical Manifestations

Early manifestations of hypercalcemia include weakness, fatigue, somnolence, irritability, headache, dizziness, muscle and bone pain, nausea, vomiting, abdominal cramps, and diarrhea or constipation. As the calcium concentration increases, hypercalcemia can induce polyuria and polydipsia. Diuresis results in salt and water depletion, further impairing calcium excretion. Severe hypercalcemia may present with ataxia, confusion, psychosis, seizure, coma, and renal failure. In addition, cardiac dysrhythmias result from a shortened refractory period and slowed conduction. ECG findings include increased PR intervals, widening of QRS complexes, QTc shortening, and flattened T waves.

Diagnostic Testing

Hypervitaminosis D should be considered in patients presenting with signs and symptoms of hypercalcemia. Laboratory results may also reveal hyperphosphatemia.

Management

Following discontinuation of vitamin D therapy and rehydration, a loop diuretic can promote calcium excretion. Corticosteroids, in doses of 100 mg/d of hydrocortisone or 20 mg/d of prednisone, and bisphosphonates, such as pamidronate and clodronate, have been used successfully in cases of severe hypercalcemia. Calcitonin, a hypocalcemic hormone, directly inhibits osteoclast activity to decrease bone resorption.

VITAMIN E

Vitamin E includes 8 naturally occurring compounds in 2 classes—tocopherols and tocotrienols—which have differing biologic activities. The most biologically active form is RRR-α-tocopherol, previously known as d-α-tocopherol, which is the most widely available form of vitamin E in food. Vitamin E deficiency occurs in patients with malabsorption syndromes. The clinical syndrome is primarily manifested by a peripheral neuropathy and spinocerebellar syndrome. Symptoms include ophthalmoplegia, hyporeflexia, gait disturbances, and decreased sensitivity to vibration and proprioception.

Pharmacology

Vitamin E absorption is dependent on the ingestion and absorption of fat and the presence of bile. Vitamin E is passively absorbed in the intestinal tract into the lymphatic circulation by a nonsaturable process.

The primary biologic function of vitamin E is as an antioxidant. It prevents damage to biologic membranes by protecting polyunsaturated fats within membrane phospholipids from oxidation. It accomplishes this task by preferentially

binding to peroxyl radicals and forming the corresponding organic hydroperoxide and tocopheroxyl radical, which, in turn, interacts with other antioxidant compounds, such as ascorbic acid, thereby regenerating tocopherol.

Pathophysiology

High doses of vitamin E may have a pro-oxidant effect. The pro-oxidant effect of vitamin E on low-density lipoproteins is related to the production of α-tocopheroxyl radicals, which are normally inhibited by other antioxidants such as vitamin C. High doses of vitamin E may displace other antioxidants, thereby disrupting the natural balance of the antioxidant system and increasing vulnerability to oxidative damage.

Clinical Manifestations

Large amounts of vitamin E, ranging from 400–800 IU/d for months to years, have been taken without any apparent harm. Vitamin E supplementation results in few obvious adverse effects, even at doses as high as 3200 mg/d. However, a recent meta-analysis reveals that at doses greater than or equal to 400 IU/d, all-cause mortality may increase.

Gastrointestinal symptoms, including nausea, diarrhea, and gastric distress are reported in patients who take excessive doses. The most significant toxic effect of vitamin E, at doses exceeding 1000 IU/d, is its ability to antagonize the effects of vitamin K. Although high oral doses of vitamin E do not typically produce a coagulopathy in normal humans who have adequate vitamin K stores, coagulopathy may develop in vitamin K-deficient patients and in those taking warfarin.

VITAMIN C

Vitamin C, also known as ascorbic acid, is ingested in the form of vitamin supplements by 35% of the US population. Vitamin C deficiency has long been recognized as the cause of scurvy. Symptoms include gingivitis, poor wound healing, bleeding, and petechiae and ecchymoses. In 80% of cases, musculoskeletal symptoms develop, consisting of arthralgia, myalgia, hemarthrosis, and muscular hematomas.

Pharmacology and Toxicokinetics

Following ingestion, intestinal absorption of vitamin C is via an active transport system that is saturable. The absorptive capacity is reached with oral ingestions of about 3 g/d. Metabolic degradation of vitamin C to oxalate accounts for 30–40% of the total daily oxalate excretion. Because metabolic conversion is saturable as well, large ingestions of vitamin C do not significantly increase oxalate production.

Vitamin C plays an important role in the synthesis of collagen, carnitine, folinic acid, and norepinephrine, as well as the processing of hormones, such as oxytocin, antidiuretic hormone, and cholecystokinin. Vitamin C also reduces iron from the ferric to the ferrous state in the stomach, thereby increasing intestinal absorption of iron.

Clinical Manifestations

The RDA for vitamin C in adults is 60 mg/d. Vitamin C is commonly taken in doses of 500 mg/d. Higher doses are fairly well tolerated as excess vitamin C

does not get absorbed or undergo metabolic degradation to oxalate to a significant extent. Thus, the possibility of oxalate nephrolithiasis should not be a significant clinical concern. Individual case reports documenting the presence of oxalate stones in the setting of vitamin C overdose have involved either intravenous administration or patients with chronic renal failure. Gastrointestinal tract effects of high doses of vitamin C may include localized esophagitis, if there is prolonged mucosal contact with ascorbic acid, and an osmotic diarrhea.

VITAMIN B_6

Pyridoxine, pyridoxal, and pyridoxamine are related compounds that share the same physiologic properties. Although all are included in vitamin B_6, the vitamin has been assigned the name *pyridoxine.* Deficiency is characterized by a seborrheic dermatitis around the eyes, nose, and mouth, cheilosis, stomatitis, glossitis, and blepharitis. More importantly, pyridoxine deficiency is associated with seizures.

Pharmacology

All forms of vitamin B_6 are well absorbed from the intestinal tract. Pyridoxine is rapidly metabolized to pyridoxal, pyridoxal phosphate (PLP), and 4-pyridoxic acid. Pyridoxal phosphate accounts for approximately 60% of circulating vitamin B_6. Most vitamin B_6 is renally excreted as 4-pyridoxic acid, with only 7% excreted unchanged in the urine.

Pyridoxal phosphate is the active form of vitamin B_6. It is a coenzyme required for the synthesis of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter. Decreased GABA formation, in the setting of pyridoxine deficiency, may contribute to seizures. Isoniazid and other hydrazines inhibit the enzyme responsible for the conversion of pyridoxine to PLP.

Pathophysiology

Neurologic symptoms characterize pyridoxine toxicity. The pathophysiology of its neurotoxicity is not well defined. Peripheral sensory nerves may be particularly vulnerable to circulating toxins because of the permeability of their associated blood vessels. These nerves lack a defense mechanism comparable to the blood–brain barrier of the central nervous system. In addition, the nerves of the CNS may be relatively shielded from pyridoxine toxicity because pyridoxine is transported into the CNS by a saturable mechanism.

Clinical Manifestations

Chronic overdoses on the order of 2–6 g/d for 2–40 months are associated with progressive sensory ataxia and severe distal impairment of proprioception and vibratory sensation. Touch, pain, and temperature sensation may be minimally impaired, and reflexes may be diminished or absent. This syndrome has since been reported with doses of pyridoxine as low as 200 mg/d. In most cases, symptoms gradually improve over several months with abstinence from pyridoxine. However, symptoms may still progress for 2–3 weeks after discontinuing pyridoxine.

Acute neurotoxicity may occur when a massive amount of pyridoxine is administered as a single dose or given over a few days. The administration of 2 g/kg of IV pyridoxine in two patients resulted in permanent dorsal root ganglia and sensory ganglia deficits.

NICOTINIC ACID

Nicotinic acid (niacin) deficiency causes pellagra, which is characterized by dermatitis, diarrhea, and dementia. In 1955, niacin was introduced as a treatment for hyperlipidemia. Nicotinic acid reduces triglyceride synthesis, with a resultant drop in very-low-density lipoprotein cholesterol and low-density lipoprotein cholesterol (LDL), and a rise in high-density lipoprotein cholesterol. Therapy is usually started with single doses of 100–250 mg. Frequency of dose and total daily dose are gradually increased until a dose of 1.5–2.0 g/d is reached. If the LDL cholesterol is insufficiently decreased with this dosing regimen, the dose is further increased to a total dose of 3.0 g/d. These doses of niacin are 100-fold higher than the amount needed to meet adult nutritional needs.

High-dose niacin has also been used as a masking agent for urine drug screens. Similar complications can occur.

Pharmacology and Toxicokinetics

Nicotinic acid is well absorbed from the intestinal tract and distributed to all tissues. With therapeutic dosing, little unchanged vitamin is excreted in the urine, but with extremely high doses the unchanged vitamin represents the major urinary component.

Clinical Manifestations

The most common adverse effects associated with the use of niacin are vasodilatory, which include cutaneous flushing and pruritus. These symptoms are mediated by prostaglandins and can occur at doses of 0.5–1.0 g/d. A single dose of aspirin taken 30 minutes before ingestion of niacin diminishes flushing.

Because rapid absorption of niacin seems to be related to the development of flushing, time-release preparations of niacin were developed. Unfortunately, these preparations are more likely to produce gastrointestinal side effects, such as epigastric distress, nausea, and diarrhea. In addition, niacin-induced hepatotoxicity occurs more frequently and is more severe in patients treated with modified-release niacin rather than immediate-release niacin.

42 Essential Oils

Essential oils are a class of aromatic hydrocarbons extracted through steam distillation or cold pressed from the leaves, flowers, bark, wood, fruit, or peel of a single parent plant. These organic compounds are a complex mixture of chemicals with structures that give the oil its aroma, therapeutic properties, and, occasionally, cause toxicity. More than 500 oils exist. They can be categorized into chemical groups: terpenes, quinines, substituted benzenes, aromatic/aliphatic esters, phenols, and aromatic/aliphatic alcohols.

With the ascent of scientific research, many essential oil remedies fell from use. More recently, trends in globalization and natural healing have led to a popular resurgence in the use of essential oils in developed countries. Essential oils are currently marketed for use in aromatherapy and certain alternative medicines.

ABSINTHE

History

Absinthe is an emerald green liqueur that is made from the extract of the wormwood plant, *Artemisia absinthium*. Many people have speculated on the cause of Vincent Van Gogh's bizarre behavior and some have concluded that his fondness for absinthe may have contributed to his seizures and episodes of psychosis.

Toxicokinetics

The toxic component in oil of wormwood is thujone, a monoterpene ketone, which exists in α and β diastereoisomeric forms. After oral absorption, both isomers undergo species-specific hydroxylation reactions by the cytochrome P450 system, followed by glucuronidation in the hepatocyte, leading to the production of several renally eliminated nontoxic metabolites.

Pathophysiology

The α-stereoisomer antagonizes the γ-aminobutyric acid type A ($GABA_A$) receptor at the picrotoxin site on the chloride channel leading to neuroexcitation. Thujones are also implicated in the development of porphyrialike syndromes, by inducing the synthesis of 5-aminolevulinic acid synthetase, leading to an increase in porphyrin production.

Clinical Features

The clinical features of acute toxicity are similar to ethanol intoxication, including euphoria and confusion, which may progress to restlessness, visual hallucinations, and delirium. Chronic abusers may suffer from seizures, hallucinations, and erratic behavior.

CAMPHOR

History

Camphor belongs to the terpene family and is capable of causing central nervous system toxicity. Camphor oil is extracted from an evergreen tree in the Laurel

family *Cinnamomum camphora*, which is native to eastern China, Japan, and Taiwan. Its primary use today is in nasal decongestant ointments such as Vicks VapoRub, although in the recent past, it was widely used in moth repellents (Chap. 99).

Toxicokinetics

Camphor is a monoterpene ketone that is rapidly absorbed from the GI tract, following which it undergoes extensive first-pass metabolism. After hydroxylation and glucuronidation in the liver, its inactive metabolites undergo urinary excretion.

Pathophysiology

Camphor is rapidly absorbed from the GI tract or through mucous membranes. Camphor is highly lipid soluble and readily crosses the blood–brain barrier and placenta. The specific neurotoxic mechanism of action has yet to be elucidated. Children seem particularly prone to hepatotoxicity and may develop a Reyelike syndrome of hepatotoxicity. It is thought that the fetus is susceptible to toxicity through the same mechanism.

Clinical Features

Camphor ingestion results in the rapid onset of nausea and vomiting, followed by headache, agitation, and seizure activity. Symptom onset usually occurs within minutes of ingestion. Seizures can occur in isolation without antecedent gastrointestinal effects. Inhalational and dermal exposures typically result in local irritation.

CLOVE

Toxicokinetics

Eugenol, a phenol, is the principal component of clove oil.

Pathophysiology

Little is known about the pathophysiology of eugenol toxicity. Intravenous infusion and intratracheal instillation of eugenol in rats has led to the development of hemorrhagic pulmonary edema, which is thought to be a result of oxidative damage.

Eugenol inhibits peripheral sensory nerve conduction at low doses, but at higher doses is associated with CNS manifestations.

Clinical Features

The topical application may result in permanent anesthesia and anhidrosis of the affected area. Likewise, inhibition of the pharyngeal reflex by inhalation of clove cigarettes may result in aspiration pneumonitis. Inadvertent oral administration of clove oil may cause marked CNS depression, metabolic acidosis, and elevation of aminotransferases.

EUCALYPTUS

Toxicokinetics

Eucalyptus oil contains up to 70% eucalyptol, a monocyclic terpene compound with an ether bridge between carbons 1 and 8. Eucalyptol is rapidly

absorbed from the gastrointestinal tract and undergoes oxidation in the liver to form hydroxycineole, and subsequently undergoes further glucuronidation and excretion. Ingestion of less than 1 teaspoon (5 mL) of eucalyptus oil has resulted in severe toxicity.

Pathophysiology

The mechanism of toxicity is unclear.

Clinical Features

Symptoms develop rapidly and include headache and lightheadedness progressing to central nervous system depression. Serious toxicity is marked by respiratory depression and vomiting, heightening the risk of aspiration.

NUTMEG

History

Nutmeg has been used as an abortifacient and abused as a hallucinogen.

Toxicokinetics

Nutmeg oil is extracted from the fruit of the evergreen tree *Myristica fragrans*. Its main active ingredient is thought to be myristicin, although other putative toxins derived from the extraction process include mace, eugenol, and other terpenes. Toxicity manifests after ingestion of 1–3 whole nuts or 1–2 tablespoons of freshly ground nutmeg.

Pathophysiology

Animal studies suggest that myristicin-induced CNS toxicity may be a result of increased concentrations of serotonin in the brain. Additionally, myristicin inhibits monoamine oxidase, which could theoretically lead to an adverse reaction if combined with another monoamine oxidase inhibitor.

Clinical Features

Central nervous system effects tend to be the predominant clinical features of toxicity. Nutmeg toxicity may mimic anticholinergic toxicity, with flushing, dryness, tachycardia, hypertension, agitation, and altered mental status. One feature that may help differentiate anticholinergic toxicity from nutmeg ingestion is that the pupils are often small.

Escalating doses result in increasing drowsiness, which may progress to coma. Abdominal pain is frequently reported, although nausea and vomiting are uncommon. The toxic syndrome typically begins in 3–6 hours after ingestion and resolves within 24 hours, although resolution may be delayed.

PENNYROYAL

Its scientific name, *Mentha pulegium* is derived from the Latin *pulex*, which means flea. Both the fresh plant and smoke from the burning leaves were used as early insect repellents, and the essential oil was used as an abortifacient and an emmenagogue.

Toxicokinetics

The active ingredient in pennyroyal oil is R-(+)-pulegone, a monoterpene commonly found in mint oils. Toxicity predominately results from ingestion of pen-

nyroyal for the purposes of inducing abortion. A human fatality was reported at an approximate dose of 500 mg/kg. Pulegone is metabolized by the cytochrome P450 system in the liver to menthofuran and other reactive metabolites.

Pathophysiology

The reactive metabolites of pulegone bind to cell proteins disrupting normal cellular function, resulting in significant cellular damage. Menthofuran also appears to be associated with pennyroyal-induced pulmonary toxicity, reflected by bronchiolar necrosis. Centrilobular hepatic necrosis is caused by depletion of hepatic glutathione by the electrophilic reactive metabolites of pulegone.

Clinical Features

Early symptoms are manifested by gastrointestinal and CNS toxicity, followed by the development of hepatic and renal dysfunction. Ingestion of 5–10 mL is associated with coma and seizures, and ingestion of 15 mL can cause death. In fatal ingestions, patients have developed disseminated intravascular coagulation and hepatic failure reflected by a purpuric rash, epistaxis, vaginal bleeding, and oozing at venipuncture sites.

PINE OIL

History

Pine oil and turpentine are distilled from the wood of pine trees. Turpentine has been historically used as a solvent and paint thinner, whereas pine oil is used as a disinfectant.

Toxicokinetics

The main active ingredient in pine oil is α-pinene, a monoterpene hydrocarbon that is absorbed via the gastrointestinal tract or through inhalation. The lipophilicity of this compound results in its accumulation in adipose tissue and slow metabolism.

Pathophysiology

Pine oil and turpentine are volatile hydrocarbon compounds with low viscosity. Inhalational injury is common when low viscosity hydrocarbons are ingested or inhaled because of inhibition of surfactant production in the alveoli. There is a significant risk of pulmonary injury associated with both pine oil and turpentine ingestion and inhalation.

Clinical Features

Pine oil ingestion results in a characteristic pine odor on the breath, whereas turpentine ingestion reportedly causes the urine to smell of violets. Significant ingestions may result in the development of central nervous system depression progressing from headache, dizziness, and blurry vision to lethargy and coma. Aspiration resulting in pneumonitis, acute lung injury, and acute respiratory distress syndrome (ARDS) is reported (Chap. 102).

WINTERGREEN

Gaultheria procumbens, a fragrant ground cover plant, is distilled to provide oil of wintergreen, which was used topically to relieve the symptoms of rheu-

matism. The active ingredient in oil of wintergreen is methylsalicylate, which has a pleasant smell and taste, posing a significant hazard to the pediatric population. Five milliliters of oil of wintergreen is equivalent in salicylate content to 7 g of aspirin.

Toxicokinetics

Methylsalicylate is rapidly absorbed from the GI tract and skin. In the liver, it undergoes hydrolysis to form salicylic acid, which then undergoes conjugation with glycine and glucuronic acid, forming salicyluric acid, salicyl acyl, and phenolic glucuronide.

Pathophysiology

Salicylate pathophysiology is extensively discussed in Chap. 35.

Clinical Features

Oil of wintergreen overdose can result in a toxic syndrome identical to that of salicylate poisoning, characterized by nausea, vomiting, tinnitus, hyperpnea, and tachypnea. Patients often present with diaphoresis and mental status changes. Severe toxicity is associated with seizures, cerebral edema, acute lung injury, coma, and death. A salicylate concentration should be determined. Chapter 35 has further details on the laboratory tests and treatment of salicylate toxicity.

DIAGNOSTIC TESTING

Laboratory studies are of limited value in essential oil toxicity. Generally, blood or urine concentrations of the active ingredients are not available in a meaningful time frame. However, the clinical status of the patient should determine which laboratory studies are ordered. Patients who present with altered mental status or seizures warrant a complete evaluation, possibly including a head CT and lumbar puncture to address other serious potential etiologies.

In patients who present with respiratory distress, chest radiographs and continuous pulse oximetry are warranted.

In a patient who ingests pennyroyal oil, a complete blood count (CBC) and liver function studies, including the aminotransferases, bilirubin, and prothrombin time (PT)/partial thromboplastin time (PTT) are indicated. In a patient who ingests oil of wintergreen, a salicylate concentration should be obtained.

TREATMENT

Treatment for patients with symptomatic essential oil toxicity is generally supportive, including the administration of intravenous fluids and supplemental oxygen. In the alert patient with an intact airway, a dose of activated charcoal may be helpful. In a patient who presents with agitation or seizures, benzodiazepines are the mainstay of treatment. Assess and treat for sequelae such as rhabdomyolysis and hepatotoxicity. *N*-acetylcysteine, in the same doses used for acetaminophen toxicity, should generally be empirically administered for prevention and treatment of hepatotoxicity from eugenol, pennyroyal, or another hepatotoxic essential oil.

43 Herbal Preparations

DEFINITION

The botanical definition of the term *herb* is specific for certain leafy plants without woody stems. However, herbal preparations often include nonherb plant materials, even animal and mineral products. Thus, broadly, herbals include any "natural" or "traditional" remedy, but these terms are also poorly defined. Many herbal preparations are purportedly used for their nonspecific "adaptogenic" properties (help the body return to a normal state by resisting stress) and lack any medicinal effects. Because many herbal users and herbalists do not consider herbal preparations as medications, the use of the term *herbal medicine* by the clinician may convey a different, and perhaps unintended, meaning.

Herbal preparations are a subset of alternative or complementary medical therapies, which themselves are defined as interventions neither widely taught in medical schools nor generally available in US hospitals. For regulatory purposes, herbal preparations are recognized by the Food and Drug Administration (FDA) as a type of dietary supplement under the Dietary Supplement Health and Education Act (DSHEA) of 1994, which reflects their classification as nutrients with nondrug status as long as the manufacturers avoid making disease-specific therapeutic claims. Given their pharmacologic constituents, it is not surprising that herbal preparations are beneficial in the treatment of certain medical conditions. However, this same concept suggests that some users will suffer adverse effects.

Up to 20% of the population use one herbal/supplement weekly, although use appears to vary greatly, depending on the community surveyed. Factors attributed to the growing use of herbals include lower cost and ease of purchase when compared to prescription medications, consumer empowerment, dissatisfaction with conventional therapies, and the perception that herbals are better and safer.

Although the FDA does not classify these preparations as medications, they are often used with the hope of preventing or treating medical illness. Despite reports of toxicity associated with their usage, no systematic evaluation of herbal efficacy or safety is required. Because patients often do not consider herbal preparations as medications, they may not provide a history of usage unless directly questioned.

PHARMACOLOGIC PRINCIPLES

The pharmacologic activity of herbal preparations (plant containing) can be classified by five active constituent classes: volatile oils, resins, alkaloids, glycosides, and fixed oils.

- Volatile oils or essential oils are aromatic plant ingredients. Many are mucous membrane irritants and have central nervous system activity. Examples include pennyroyal oil (*Mentha pulegium*) and catnip (*Nepeta cataria*) (Chap. 42.)
- Resins are complex chemical mixtures of acrid resins, resin alcohols, resinol, tannols, esters, and resenes. These substances are often strong gastrointestinal irritants. An example is black cohosh root (*Cimicifuga racemosa*).

- Alkaloids are a heterogeneous group of alkaline, organic, and nitrogenous compounds. The alkaloid compound is usually found throughout the plant. Examples include aconitum (*Aconitum napellus*) and jimson weed (*Datura stramonium*).
- Glycosides are esters that contain both a sugar (glycol) and a nonsugar (aglycone) component, which yields one or more sugars during hydrolysis. Examples include cyanogenic glycosides found in apricot, cherry, and peach pits, and cardiac glycosides (cardioactive steroids) (Chap. 62) found in foxglove (*Digitalis* spp).
- Fixed oils are esters of long-chain fatty acids and alcohols. Herbs containing fixed oils are generally used as emollients, demulcents, and bases for other agents. Generally, these are not toxic. An example is olive oil (*Olea europaea*).

FACTORS CONTRIBUTING TO HERBAL TOXICITY

The toxicity of a plant may vary widely and depends on certain conditions, such as the time of year, developmental stage at harvest, growing conditions and locale, storage environment, and part of the plant consumed. Poisonings are most likely to result from the misuse, misidentification, misrepresentation, or contamination of the product. Metal poisonings by lead, cadmium, mercury, copper, zinc, and arsenic may occur. These may be contaminants or intentionally included for purported medicinal benefit. Patent herbals may also contain surreptitious pharmaceuticals, such as acetaminophen, which are generally not listed on the packaging.

CLASSIFICATION OF TOXICITY

Herbal preparations are associated with a wide variety of toxicologic manifestations (Table 43–1). In addition, many individual herbal preparations are associated with multiple types of toxicologic effects. To better understand these effects, it is useful to organize herbal toxicity into several general categories.

Indirect Health Risks

Herbal usage may adversely impact health by altering previous conventional prescription medication therapy. This may occur as a result of a change in compliance with an existing regimen, or an alteration in the pharmacology of the conventional medication.

Direct Health Risks

Direct health risks include pharmacologically predictable and dose-dependent toxic reactions and unpredictable idiosyncratic effects. Long-term and delayed toxic effects include organ dysfunction and carcinogenesis.

TOXICITY OF SPECIFIC HERBAL PREPARATIONS

Cardiovascular Toxins

Aconite

Aconites (caowu, chuanwu, and fuzi) are the dried rootstocks of the *Aconitum* plant. Aconitine is an alkaloid that increases sodium influx through the myocardial sodium channel, increasing inotropy, while delaying the final re-

TABLE 43–1. Selected Herbal Preparations, Popular Use, and Potential Toxicities

Herbal Preparation	Scientific Name	Other Common Names	Traditional and Popular Usage	Toxic Ingredient(s)	Adverse Effects
Aconite	*Acontium napellus kusnezoffi, carmichaelii*	Monkshod, wolfsbane caowu, chuanwu, bushi	Topical analgesic; neuralgia, asthma, and heart disease	Aconite alkaloids (C19 diterpenoid esters)	Gastrointestinal upset, dysrhythmias
Aloe	*Aloe vera* and other spp	Cape, zanzibar, socotrine, curacao, carrisyn	Heals wounds, emollient, laxative, abortifacient	Anthraquinones barbaloin, isobarbaloin	Gastrointestinal upset, dermatitis
Apricot pits	*Prunus armeniaca*	—	Laetrile (cancer remedy)	Amygdalin	Cyanide poisoning
Aristolochia	*Aristolochia clematis, Aristolochia reticulata*	Birthwort, hearwort, fangchi	Uterine stimulant	Aristolochic acid	Nephrotoxin
Astragalus	*Astragalus membranaceus*	Huang qi, milk vetch root	Immune booster, AIDS, cancer, antioxidant, increase endurance	—	May alter effectiveness immunosuppressives (eg, steroids, cyclosporine)
Atractylis	*Atractylis gummifera*	Piney thistle	Chewing gum, antipyretic, diuretic, gastrointestinal remedy	Potassium atractylate and gummiferin: mitochondrial toxin	Hepatitis, altered mental status, seizures, vomiting, hypoglycemia
Atractylodes	*Atractylodes macrocephala*	Baizhu, cangzhu	Appetite stimulant, diuretic, GI upset	—	None
Autumn crocus	*Colchicum autumnale*	Crocus, fall crocus, meadow saffron, mysteria, vellorita	Gout, rheumatism, prostate/hepatic disease, cancer, gonorrhea	Colchicine	Gastrointestinal upset, renal disease, agranulocytosis
Betel nut	*Areca catechu*	Areca nut, pinlang, pinang	Stimulant	Arecholine	Possible bronchospasm, chronic use associated with leukoplakia and squamous cell carcinoma

(continued)

TABLE 43–1. Selected Herbal Preparations, Popular Use, and Potential Toxicities *(continued)*

Herbal Preparation	Scientific Name	Other Common Names	Traditional and Popular Usage	Toxic Ingredient(s)	Adverse Effects
Black cohosh	*Cimicifuga racemosa*	Black snakeroot, squawroot, bugbane, baneberry	Abortifacient, menstrual irregularity, astringent, dyspepsia	—	Dizziness, nausea, vomiting, headache
Blue cohosh	*Caulophyllum thalictroides*	Squaw root, papoose root	Abortifacient, menstrual disorders, antispasmodic	*N*-methylcytisine ($^1/_{40}$ potency of nicotine)	Nicotinic toxicity
Borage	*Borago officinalis*	—	Diuretic, antidepressant, antiinflammatory	Pyrrolizidine alkaloids, amabiline	Hepatotoxicity
Broom	*Cytisus scoparius*	Bannal, broom, broom top	Cathartic, diuretic, induce labor, drug of abuse	L-Sparteine	Nicotinelike poisoning
Buckthorn	*Rhamnus fangula*	—	Laxative	Anthraquinones	Diarrhea, weakness
Burdock root	*Arctium lappa, Arctium minus*	Great burdock, gobo, lappa, beggar's button, hareburr, niu bang zi	Diuretic, cholerectic, induce sweating, remedy for skin disorders, burn remedy	Atropine (possible contaminant)	Anticholinergic toxicity
Cantharidin	*Cantharidin* beetle	Spanish fly, blister beetles	Aphrodisiac, abortifacient, blood purifier	Terpenoid: cantharidin	Gastrointestinal upset, urinary tract and skin irritant, renal toxicity
Cascara	*Cascara sagrada*	—	Laxative	Anthraquinones	Diarrhea, weakness
Catnip	*Nepeta cataria*	Cataria, catnep, catmint	Indigestion, colic, sedative, headaches, emmenagogue	Nepetalactone	Sedative
Ch'an Su	*Bufo gargarizans, Bufo melanosticus*	Stone, lovestone, black stone, rock hard, chu an wu, kyushin	Topical anesthetic, aphrodisiac, cardiac disease	Bufadienolides bufotenin	Dysrhythmias, hallucinations

Chamomile	*Chamomilla recutita, Chamomilla nobile*	Manzanilla	Digestive disorders, skin disorders, cramps	Allergens	Contact dermatitis, allergic reaction, anaphylaxis very rare
Chaparral	*Larrea tridentata*	Creosote bush, greasewood, hediondilla	Bronchitis, analgesic, retard aging, possible cancer treatment	Nondihydroguaiaretic acid (NDGA)	Hepatotoxicity (chronic)
Chestnut	*Aesculus* spp	Horse chestnut, California buckeye, Ohio buckeye, buckeye	Arthritis, rheumatism, varicose veins, hemorrhoids	Esculin, nicotine, quercetin, quercitrin, rutin, saponin, shikimic acid	Fasciculations, weakness, incoordination, gastrointestinal upset, paralysis, stupor
Clove	*Syzygium aromaticum*	Caryophyllum	Expectorant, antiemetic, counterirritant, antiseptic, carminative	Eugenol (4-allyl-2-methoxyphenol)	Pulmonary toxicity (cigarettes)
Comfrey	*Symphytum officinale* and other species, *S. xuplandicum*	Knitbone, bruisewort, blackwort, slippery root, Russian comfrey	Ulcers, hemorrhoids, bronchitis, heal burns, sprains, swelling, bruises	Pyrrolizidine alkaloids: symphytine, exhimidine, lasiocarpine	Hepatic venoocclusive disease, hepatocellular adenomas (rats)
Compound Q	*Trichosanthes kirilowii*	Gualougen, GLQ-223, chinese cucumber root	Fevers, swelling, expectorant, abortifacient, diabetes, AIDS	Trichosanthin	Pulmonary and cerebral edema, cerebral bleed, seizures, fevers
Dong Quai	*Angelica polymorpha*	Tang kuei, dang gui	Blood purifer, menstrual disorders, improve circulation	Coumarin, psoralens, safrole in essential oil	Anticoagulant effects, photodermatitis; possible carcinogen in oil
Echinacea	*Echinacea angustifolia, Echinacea purpurea*	American cone flower, purple cone flower, snakeroot	Infections, immunostimulant	—	None
Elder	*Sambucus* spp	Elderberry, sweet elder, sambucus	Diuretic, laxative, astringent, cancer	Cyanogenic glycoside sambunigrin in leaves	Gastrointestinal upset, weakness if ingesting uncooked leaves

(continued)

TABLE 43–1. Selected Herbal Preparations, Popular Use, and Potential Toxicities *(continued)*

Herbal Preparation	Scientific Name	Other Common Names	Traditional and Popular Usage	Toxic Ingredient(s)	Adverse Effects
Ephedra	*Ephedra* spp	Ma-huang, Mormon tea, yellow horse, desert tea, squaw tea	Stimulant, bronchial disorders	Ephedrine pseudoephedrine	Headache, insomnia, dizziness, palpitations, seizures, stroke, myocardial infarction, death
Feverfew	*Tanacetum parthenium*	Featherfew, altamisa, bachelor's button, featherfoil, febrifuge plant, midsummer daisy, nosebleed, wild quinine	Migraine headache, menstrual pain, asthma, dermatitis, arthritis, antipyretic, abortifacient	—	Oral ulcerations, "postfeverfew syndrome" rebound of migraine symptoms, anxiety, and insomnia following cessation of use
Garlic	*Allium sativum*	Allium, stinking rose, rustic treacle, nectar of the gods, da suan	Infections, coronary artery disease, hypertension	Ajoene	Contact dermatitis, gastroenteritis, antiplatelet effects
Germander	*Teucrium chamaedrys*	Wall germander	Relief of fever, abdominal disorders, wounds, diuretic, choleretic	—	Hepatitis, cirrhosis
Ginger	*Zingiber officinale*	—	Carminative, diuretic, antiemetic stimulant, motion sickness	Volatile oil, phenol	Possible increased risk of bleeding when taken with anticoagulants
Ginkgo	*Ginkgo biloba*	Maidenhair tree, kew tree, tebonin, tanakan, rokan, kaveri	Asthma, chilblains, digestive aid, cerebral dysfunction	Ginkgolides	Extracts: gastrointestinal upset, headache, skin reaction; whole plants allergic reactions

Ginseng	*Panax ginseng, P. quinquefolius, P. pseudoginseng*	Ren shen	Respiratory illnesses, gastrointestinal disorders, impotence fatigue, stress, adaptogenic, external demulcent	—	Ginseng abuse syndrome
Glucosamine	2-Amino-2-deoxyglucose	Chitosamine	Wound-healing polymer, antiarthritic	—	None
Goat's rue	*Galega officinalis*	French lilac, French honeysuckle	Antidiabetic	Galegine, paragalegine	Hypoglycemia
Goldenseal	*Hydrastis canadensis*	Orange root, yellow root, tumeric root	Astringent, gastrointestinal disorders, menstrual bleeding	—	Gastrointestinal upset, paralysis, respiratory failure
Gordolobo yerba	*Senecio longiloba, S. aureus, S. vulgaris, S. spartoides*	Groundsel, life-root	To gargle, for cough, emmenagogue	Pyrrolizidine alkaloids	Hepatic venoocclusive disease
Heliotrope	*Crotalaria specatabilis, Heliotropium europaeum*	Rattlebox, groundsel, viper's bugloss, bush tea	—	Pyrrolizidine alkaloids	Hepatic venoocclusive disease
Impila	*Callipesis laureola*	—	Zulu traditional remedy	Potassium atractylate-like compound	Vomiting, hypoglycemia, centrilobular hepatic necrosis
Jimson weed	*Datura stramonium*	Datura stramonium, apple of Peru, Jamestown weed, thornapple, tolguacha	Asthma	Atropine, scopolamine, hyoscyamine, stramonium	Anticholinergic toxicity
Kava kava	*Piper methysticum*	Awa, kava-kava, kew, tonga	Relaxation beverage, uterine relaxation, headaches, colds, wounds, aphrodisiac	Flavokwain A and B Kava lactones	Skin discoloration, hepatic failure Euphoria, muscle weakness

(continued)

TABLE 43–1. Selected Herbal Preparations, Popular Use, and Potential Toxicities *(continued)*

Herbal Preparation	Scientific Name	Other Common Names	Traditional and Popular Usage	Toxic Ingredient(s)	Adverse Effects
Kola nut	*Cola acuminata*	Botu cola, cola nut	Digestive aid, tonic, aphrodisiac, headache, diuretic	—	CNS stimulant
Kombucha	Mixture of bacteria and yeast	Kombucha tea, kombucha mushroom, Manchurian tea	Memory loss, premenstrual syndrome, cancer	—	None
Licorice	*Glycyrrhiza*	Spanish licorice, Russain licorice, gancao	Gastric irritation	Glycoside glycyrrhizin	Flaccid weakness, hypokalemia, lethargy
Lobelia	*Lobelia inflata*	Indian tobacco	Antispasmodic, respiratory stimulant, relaxant	Pyridine-derived alkaloids (lobeline)	Nicotine toxicity
Mace	*Myristica fragrans*	Mace, muscade, seed cover of nutmeg	Diarrhea, mouth sores, insomnia, rheumatism	Myristicin (methoxysafrole)	Hallucinations
Mate	*Ilex paraguayensis*	Paraguay tea	Stimulant (caffeine)	—	CNS stimulant
Milk thistle	*Carduus marianus, Silybum marinaum*	Mary thistle	Liver disease, antidepressant, HIV	—	None
Pau d'Arco	*Tabebuia* spp	Ipe roxo, lapacho, taheebo tea	Tonic, blood builder, cancer, AIDS	Naphthoquinone derivative: lapachol	Gastrointestinal upset, anemia, bleeding
Pennyroyal oil	*Hedeoma pulegioides, Mentha pulegium*	American pennyroyal, Squawmint, mosquito plant	Abortifacient, regulate menstruation, digestive tonic	Pulegone, menthofuran	Hepatotoxicity
Periwinkle	*Catharanthus roseus*	Red periwinkle, Madagascar or Cape periwinkle	Ornamental, ocular inflammation, diabetes, hemorrhage, insect stings, cancers	Vincristine, vinblastine	Vincristine/vinblastine toxicity

Podophyllum	*Podophyllum peltatum, Podophyllum hexandrum, Podophyllum emodi*	Mandrake, mayapple, American podophyllum, Indian podophyllum, guijiu	Cathartic, purgative	Podophyllin	Podophyllin toxicity
St. John's wort	*Hypericum perforatum*	Klamath weed, John's wort, goatweed, sho-ren-gyo	Anxiety, depression, gastritis, insomnia, promote healing, AIDS	Hyperforin	Occasional photosensitization, drug interactions: CYP3A4
Salvia	*Salvia divinorum*	Sierra mazateca, diviners sage, magic mint, Maria pastora	Hallucinogen	Salvinorum A	Hallucinations
Saw Palmetto	*Serenoa repens*	Sabal, American dwarf palm tree, cabbage palm	Genitourinary disorders, increase sperm production, sexual vigor	—	Diarrhea
Senna	*Cassia acutifolia, Cassia angustifolia*	Alexandrian senna	Stimulant, laxative, diet tea	Anthraquinone, glycosides (sennosides)	Diarrhea, CNS effects, mellanosis coli
Shark cartilage	*Squalus acanthias, Sphyrna leewini*	—	Cancer: inhibit tumor angiogenesis	—	None
Siberian ginseng	*Acanthopanax senticos*	Devil's shrub, eleuthera, eleutherococ	Adaptogens, hypertension, immune system stimulant	—	None
Slippery Elm	*Ulmus rubra, Ulmus fulva*	Elm, elm bark, red elm	Acne, boils, indigestion, abortifacient	Oleoresin	Contact dermatitis
SOD	Superoxide dismutase	Orgotein, ormetein, palosein	Improve health, lengthen life span, chronic bladder disease, paraquat poisoning	—	None

(continued)

TABLE 43–1. Selected Herbal Preparations, Popular Use, and Potential Toxicities *(continued)*

Herbal Preparation	Scientific Name	Other Common Names	Traditional and Popular Usage	Toxic Ingredient(s)	Adverse Effects
Soy isoflavone	*Glycine max*	—	Menopausal symptoms, heart disease	Phytoestrogens: genistein, daidzein, glycitein	Risk of cancer
Squill	*Urginea maritima, Uriginea indica*	Sea onion	Diuretic, emetic, cardiotonic, expectorant	Cardioactive steroid, scillaren A	Emesis
Stephania	*Stephani tetrandra*	Han fang ji	Fever, pain, inflammation, decrease water retention	—	None (misidentification of this herb with aristolochia [Guang fang ji] resulted in cases of Chinese herb neuropathy)
Stevia	*Stevia rebaudiana*	Sweet leaf of Paraguay	Sugar-free sweetener, diabetes, hypertension, weight-loss aid	Stevioside	None
Tonka bean	*Dipteryx odorata, Dipteryx oppositifolia*	Tonquin bean, cumaru	Food, cosmetics	Coumarin	Anticoagulant effect
Tung seed	*Aleurities moluccana*	Tung, candlenut, candleberry, barnish tree, balucanat, otaheite	Wood preservative (oil), purgative (oil), asthma treatment (seed)	—	Gastrointestinal upset, hyporeflexia, death; latex dermatitis
Valerian	*Valeriana officinalis*	Radix valerianae, Indian valerian, red valerian	Anxiety, insomnia, antispasmodic	—	Hepatotoxicity
White willow bark	*Salix alba*	Common willow, European willow	Fever, pain astringent	Salicin	Salicylate toxicity
Wild lettuce	*Lactuca virosa*	Lettuce opium, prickly lettuce	Sedative, cough suppressant, narcotic substitute	—	None

Woodruff	*Galium odoratum*	Sweet woodruff	Wound healing, tonic, varicose vein treatment, antispasmodic	Coumarin	None
Wormwood	*Artemisia absinthium*	Absinthe	Sedative, analgesic, antihelminthic	Thujone	Psychosis, hallucinations, seizures
Yew	*Taxus baccata*	Yew	Antispasmodic, cancer remedy	Taxine (Na^+ channel blocker)	Dizziness, dry mouth, bradycardia, cardiac arrest
Yohimbe	*Pausinystalia yohimbe*	Yohimbi, yohimbehe	Body building, aphrodisiac, hallucinogen	Alkaloid yohimbine from bark	Hypotension, abdominal pain, weakness, paralysis

polarization phase of the action potential and promoting premature excitation. Sinus bradycardia and ventricular dysrhythmias can occur. Although there is no antidote available, anecdotal reports suggest the use of amiodarone, flecainide, bretylium, lidocaine, and procainamide for ventricular tachydysrhythmias.

Ch'an Su

Ch'an Su is a traditional herbal remedy for congestive heart failure derived from the secretions of the parotid and sebaceous glands of a toad, *Bufo bufo gargarizans* or *Bufo melanosticus*. Ch'an Su contains both digoxinlike cardioactive steroids and a hallucinogenic compound, bufotenin. Clinical findings following ingestion are similar to cardioactive steroid poisoning, including gastrointestinal symptoms and dysrhythmias. Ch'an Su was marketed as a topical aphrodisiac and resulted in a number of digoxinlike fatalities. Assays for serum digoxin unpredictably cross-react with Ch'an Su and digoxin-specific Fab was successfully used to treat its poisoning.

Central Nervous System Toxins

Absinthe

Wormwood (*Artemisia absinthium*) extract is the main ingredient in absinthe, a toxic liquor that was outlawed in the United States in 1912. This volatile oil is a mixture of α- and β-thujone. Chronic absinthe use causes absinthism, which is characterized by psychosis, hallucinations, intellectual deterioration, and seizures. Treatment remains supportive.

Anticholinergic Agents: Henbane, Jimson Weed, Mandrake

Many plants contain the belladonna alkaloids: atropine (DL-hyoscyamine), hyoscyamine, and scopolamine (L-hyoscine). Signs and symptoms of anticholinergic poisoning include mydriasis, diminished bowel sounds, urinary retention, dry mouth, flushed skin, tachycardia, and agitation. Mildly poisoned patients usually require only supportive care and sedation with intravenous benzodiazepines. Intravenous physostigmine reverses anticholinergic poisoning.

Ephedra

Ephedra species contain the alkaloids, ephedrine and, in some species, pseudoephedrine. In large doses, ephedrine causes anxiety, insomnia, palpitations, restlessness, mania, and psychosis. The most consequential concern is hypertension with subsequent cardiovascular and cerebrovascular injury. The treatment is similar to that for other CNS stimulants. In 2002, the FDA banned the sale of ephedra-containing dietary supplements, although subsequent rulings permitted limited availability of ephedra-like alkaloids.

Nicotinic Agents: Betel Nut, Blue Cohosh, Broom, Chestnut, Lobelia, Tobacco

Betel (*Areca catechu*) is chewed by an estimated 200 million people worldwide for its euphoric effect. The active ingredient is arecoline, a direct-acting nicotinic agonist, very similar to nicotine in cigarette tobacco. Arecoline may cause exacerbation of bronchospasm in asthmatic patients chewing betel nut. Treatment for betel nut toxicity is supportive. Many other herbal preparations have nicotinic-effects and produce similar clinical findings.

Hepatotoxins

Pennyroyal

Pennyroyal oil is a volatile oil extract from the leaves of *Mentha pulegium* and *Hedeoma pulegioides* plants. Herbalists use pennyroyal oil as an abortifacient and to regulate menstruation. However, pulegone, the active volatile oil, causes direct hepatotoxicity following glutathione depletion, which occurs after metabolism to menthofuran. Because pulegone is similar to acetaminophen in its mechanism of toxicity, *N*-acetylcysteine treatment may be beneficial.

Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids are hepatotoxins that undergo metabolism to pyrroles, which serve as biologic alkylating agents. The pyrroles cause hepatic sinusoidal hypertrophy and venous occlusion, resulting in hepatic venoocclusive disease, hepatomegaly, cirrhosis, and, possibly, hepatic carcinoma. Pulmonary toxicity resulting in pulmonary artery hypertension and right ventricular hypertrophy also may occur.

Metals

Poisonings by metals, including arsenic, cadmium, lead, and mercury, may occur following consumption of various types of herbal preparations. Treatment consists of cessation of the herbal product and use of an appropriate chelating agent when indicated. Pay-Loo-Ah, a red and orange powder used by the Hmong people as a fever and rash remedy, was contaminated with lead. Ayurvedic remedies, based upon ancient traditional healing of India, often intentionally contain metals such as gold, silver, copper, zinc, iron, lead, tin, and mercury. Azarcon (lead tetroxide) and Greta (lead oxide) are widely used in Mexico for treatment of *empacho* (“chronic digestive problem”).

Renal Toxins

Aristolochia

Aristolochic acid in aristolochia (*Aristolochia fangchi*) causes renal fibrosis with chronic use. Patients with aristolochia-induced nephropathy also have an increased risk for developing urothelial cancer.

Chinese Patent Medications

Chinese patent medicines, a component of traditional Chinese medicine, contain traditional herbals, formulated into tablets, capsules, syrups, powders, ointments, and plasters for easy use. They are produced by poorly regulated Chinese pharmaceutical companies and are very susceptible to adulteration or contamination. They are often sold by nonherbalists at convenience stores in packages with incomplete documentation of ingredients and they are typically not labeled in English. They appear to be very susceptible to adulteration with potentially dangerous pharmaceuticals, such as phenylbutazone.

TREATMENT

A specific treatment strategy should emphasize identification of the specific herbal preparation(s) used by the patient, concurrent medication(s), and med-

ical illness(es). Because herbal preparation toxicity varies greatly depending on the preparation used, careful examination may be aided by knowledge of the herbal preparation. In most cases, supportive care and discontinuation of the herbal preparation(s) is sufficient. Some herbal toxicities may require specific laboratory analysis and therapy.

All adverse events associated with herbal preparations should be reported to the local poison control center or to FDA MedWatch by phone at 1-800-FDA-1088 or online at https://www.fda.gov/medwatch.

44 Athletic Performance Enhancers

The desire to improve athletic performance by using pharmacologics is a relatively recent development in history. Public interest in extraordinary athletic achievement fuels the modern-day science of performance enhancement in sports. The word "doping" comes from the Dutch word "doop," a viscous opium juice used by the ancient Greeks.

HISTORY AND EPIDEMIOLOGY

Controversy surrounding the systematic use of performance-enhancing drugs by athletes has marred many sporting events. Since the International Olympic Committee (IOC) began testing for drugs during the 1968 Olympic games, prominent athletes have been sanctioned and even stripped of their Olympic medals as a result of testing positive for banned substances. However, from a public health perspective, the use of performance-enhancing drugs among athletes of all ages and abilities is a far more serious concern than the highly publicized cases involving a few world-class athletes. The majority of studies on the epidemiology of performance-enhancing substances have investigated androgenic ("masculinizing") anabolic ("tissue building") steroid use. Studies of high school students document that 6.6% of male seniors have used anabolic steroids and 35% of these individuals were not involved in organized athletics.

PRINCIPLES

There are several ways to classify performance enhancers for the purposes of study. Some categorize agents according to the expected effect of the drug. For example, some xenobiotics increase muscle mass, whereas others decrease recovery time, increase energy, or mask the presence of other drugs. However, one drug may have several expected effects. According to the World Anti-Doping Agency (WADA) code, a substance or method constitutes doping and can be added to the prohibited list if it meets 2 of the following 3 criteria: it is performance enhancing, its use presents a danger to the health of the athlete, and it is contrary to the spirit of sport (Table 44–1).

ANABOLICS

Androgenic Steroids

Androgenic anabolic steroids (AAS) increase muscle mass and lean body weight, and cause nitrogen retention. Testosterone is the prototypical androgen; most androgenic anabolic steroids are synthetic testosterone derivatives. The androgenic effects of steroids are responsible for male appearance and secondary sexual characteristics, such as increased growth of body hair and subsequent deepening of the voice.

TABLE 44–1. Abbreviated Summary of World Anti-Doping Agency 2005 Prohibited List

Substances (S) and Methods (M) Prohibited at All Times (In- and Out-of-Competition)
S1. Anabolic agents
S2. Hormones and related substances
S3. β-Adrenergic agonists
S4. Agents with antiestrogenic activity
S5. Diuretics and other masking agents
M1. Enhancement of oxygen transfer
M2. Chemical and physical manipulation
M3. Gene doping
Substances and Methods Prohibited In-Competition
In addition to S1 to S5 and Ml to M3 above, the following categories are prohibited in competition:
S6. Stimulants
S7. Narcotics
S8. Cannabinoids
S9. Glucocorticosteroids
Substances Prohibited in Particular (P) Sports
P1. Alcohol
P2. β-Adrenergic antagonists
Specified Substances[a]
Ephedrine
Cannabinoids
All inhaled β_2-adrenergic agonists, except clenbuterol
Probenecid
All glucocorticosteroids
All β-adrenergic antagonists
Alcohol

[a]In certain circumstances, a doping violation involving specified substances may result in a reduced sanction, provided the athlete establishes that the use was not intended to enhance performance.

Physiology and Pharmacology

The Leydig cells of the testis produce 95% of endogenous male testosterone; the remainder comes from the adrenal glands. Normally, 4–10 mg of testosterone and 1–3 mg of androstenedione are produced daily in men. Women secrete about 0.04–0.12 mg of testosterone, as well as 2–4 mg of androstenedione daily from their ovaries and adrenal glands.

Testosterone is rapidly degraded in the liver. The plasma half-life is less than 30 minutes. Consequently, to create a substance that is useful clinically, testosterone is esterified at the 17-hydroxy position, forming a hydrophobic compound that can be administered in an oil vehicle for gradual release. Most of these esters of testosterone must be injected intramuscularly to avoid extensive first-pass hepatic metabolism associated with oral administration. The alternative to esterification at the 17-hydroxy position is to alkylate the position. Alkylated androgens may be administered orally because they are more resistant to hepatic metabolism.

Antiestrogens and Antiandrogens

In sports, the general purpose for taking androgens is to increase the anabolic effects and to avoid the unwanted side effects of feminization, such as gynecomastia, or masculinizing secondary sexual characteristics such as facial hair and deepening voice. Because it is impossible to completely dissociate the desired from undesired effects of androgens, athletes use agents to manipulate the pathways of androgen metabolism to decrease unwanted side effects by combining xenobiotics with antiestrogenic or antiandrogenic activity. Such xenobiotics are divided into aromatase inhibitors such as anastrozole (Arimidex) and aminoglutethimide (Cytadren), selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene, and other antiestrogenic compounds such as clomiphene (Clomid).

Clinical Manifestations of Androgenic Anabolic Steroids

When combined with strength training, supraphysiologic doses of testosterone increase muscle strength and size. The most common musculoskeletal complications of steroid use are tendon and ligament rupture.

Hepatic subcapsular hematoma with hemorrhage is also reported. Peliosis hepatis, a condition of blood-filled sinuses in the liver that may result in fatal hepatic hemorrhage, occurs most commonly with alkylated androgens and may not improve when androgen use is stopped.

Local complications from injection include infected joints, cutaneous abscess, and *Candida albicans* endophthalmitis. Injection of steroids with contaminated needles has led to the transmission of infectious diseases such as HIV, hepatitis B, and hepatitis C.

Cutaneous side effects are common and include keloid formation, sebaceous cysts, comedones, seborrheic furunculosis, folliculitis, and striae. Acne is associated with steroid use and is sometimes referred to as "gymnasium acne." A common triad of acne, striae, and gynecomastia occurs.

The conversion of AAS to estradiol in peripheral tissues results in the feminization of male athletes. Gynecomastia may be irreversible. AAS use also causes testicular atrophy and decreased spermatogenesis, which may be reversible. In females menstrual irregularities, breast atrophy, and virilization may occur.

Cardiac complications include acute myocardial infarction and sudden cardiac arrest. Autopsy examination of the heart may reveal biventricular hypertrophy, extensive myocardial fibrosis, and contraction band necrosis. In addition to direct myocardial injury, vasospasm or thrombosis may occur. Alkylated androgens lower high-density lipoprotein (HDL) cholesterol and may increase platelet aggregation. Thromboembolic events, such as pulmonary embolus, stroke, carotid arterial occlusion, and cerebral sinus thrombosis, are well described.

Distractibility, depression or mania, delirium, irritability, insomnia, hostility, anxiety, mood lability, and aggressiveness ("roid rage") may occur. These neuropsychiatric effects do not appear to be correlated with plasma AAS concentrations. Withdrawal symptoms from AAS include decreased libido, fatigue, and myalgias.

Clenbuterol

Clenbuterol is a β_2- and β_3-adrenergic agonist that decreases fat deposition and prevents protein breakdown in animal models. Clenbuterol is also a potent *nutrient partitioning agent,* a term implying that it is able to increase the

amount of muscle and decrease the amount of fat produced per pound of feed given to cattle and other animals. Clenbuterol increases the glycolytic capacity of muscle and causes hypertrophy, enhancing the growth of fast-twitch fibers. Clenbuterol overdose is characterized by the typical symptoms of sympathomimetic overdose.

PEPTIDES AND GLYCOPROTEIN HORMONES

Creatine

Creatine is an amino acid that is synthesized naturally by the liver, kidneys, and pancreas from the amino acids methionine, arginine, and glycine. In its phosphorylated form, it is involved in the resynthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP). Because ATP is the immediate source of energy for muscle contraction, creatine is used by athletes to increase energy during short, high-intensity exercise. Numerous studies demonstrate improved performance with creatine supplementation, particularly in those sports requiring short, high-intensity effort.

One adverse effect of creatine supplementation is weight gain. It is thought that this is primarily a result of water retention. However, there is evidence that net protein increase is partially responsible for the weight gain with the long-term use of creatine. Creatine supplementation increases urinary creatine and creatinine excretion, and may increase serum creatinine concentrations by 20%. However, long- and short-term creatine supplementation does not appear to affect renal function adversely.

Human Growth Hormone

Human growth hormone (hGH) is an anabolic peptide hormone secreted by the anterior pituitary gland. It causes its anabolic effect by stimulating protein synthesis and by increasing growth and muscle mass in children. Recombinant human growth hormone has been available since 1984, and it is commonly used therapeutically for children with growth hormone deficiency in daily doses of 5–26 μg/kg body weight. The effects on increasing muscle mass and size are well proven in growth hormone-deficient individuals, but studies do not support a resultant increase in strength related to this increase in muscle size.

Human growth hormone administration can cause myalgias, arthralgias, carpal tunnel syndrome, and edema. Growth hormone can also cause glucose intolerance and hyperglycemia. Skin changes occur, such as increased melanocytic nevi and change in skin texture. Lipid profiles may be adversely affected. HDLs are decreased, a change associated with increased risk of coronary artery disease. Because hGH must be given parenterally, there is a risk of transmission of infection.

Insulinlike Growth Factor

Insulinlike growth factor type 1 (IGF-1) is a peptide chain structurally related to insulin. IGF-1 is approved for the parenteral administration for the clinical treatment of dwarfism and insulin resistance. The effects of growth hormone are primarily mediated by IGF-1. IGF-1 binds principally to the type I IGF receptor, which has 40% homology with the insulin receptor and a similar tyrosine kinase subunit. IGF-1 increases glucose use by causing the movement of glucose into cells, increasing amino acid uptake, and stimulating protein synthesis.

Side effects are similar to those associated with the use of growth hormone and include acromegaly. Other effects include headache, jaw pain, edema, and adverse alterations in lipid profiles. A potentially serious side effect of IGF-1 is hypoglycemia.

Insulin

Insulin is used by body builders for its anabolic properties. Hypoglycemia is the obvious complication (Chap. 48).

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a glycoprotein that stimulates testicular steroidogenesis in men and may be used by male athletes to prevent testicular atrophy during and after androgen administration. Although administration of hCG causes an increase in the total testosterone produced, the testosterone-to-epitestosterone ratio is unchanged as epitestosterone production is also stimulated.

OXYGEN TRANSPORT

Erythropoietin

Erythropoietin (EPO) induces erythropoiesis by a receptor-mediated mechanism that stimulates stem cells to develop into mature red blood cells. EPO increases exercise capacity and hemoglobin production and is used by athletes, often with additional iron supplementation. The clinical effects of increased hematocrit occur several days after the administration, and oxygen uptake increases by 6–7%.

Erythropoietin enhances endothelial activation and platelet reactivity and increases the systolic blood pressure during submaximal exercise. These effects, in addition to the increase in hemoglobin, increase the risk for thromboembolic events, hypertension, and hyperviscosity syndromes. Increases in hematocrit subsequent to erythropoietin use are believed to have contributed to the deaths of a number of competitive cyclists in Europe.

Clinical manifestations of overdose include confusion, a plethoric appearance, signs of hyperviscosity, and tissue ischemia or infarction. Hematocrits as high as 72% have been reported following intentional overdose. Emergent phlebotomy and erythropheresis can result in rapid reduction of the hematocrit and improvement in the patient's condition.

Artificial Oxygen Carriers

Artificial oxygen carriers are blood substitutes that supplement the oxygen-carrying capacity of red blood cells. Artificial oxygen carriers fall into two categories: hemoglobin-based oxygen carriers (HBOCs) or perfluorocarbon emulsions. Athletes may experiment with these substances to increase endurance. Hemoglobin may be genetically engineered or obtained from cattle or outdated blood. Perfluorocarbons (PFCs) are synthetic oxygen-carrying compounds that can be used as red blood cell substitutes. These liquids, composed of 8–10 carbon atoms with fluorine substitution for hydrogen, serve as excellent solvents for gases.

Several cyclists have been hospitalized for illnesses that were possibly associated with PFC use. Symptoms included transient back pain, malaise, flushing, and fever of several hours duration. Dose-related thrombocytopenia

is transient and occurs 3–4 days after administration. PFCs increase vascular tone, which can cause hypertension. Both systemic and pulmonary vascular resistance is increased. For unclear reasons, intravenous infusion of these emulsions can sometimes cause cardiac arrest. Allergic reactions are reported to the egg yolk emulsifying agent.

The infusion of autologous or heterologous blood for the purpose of increasing the hematocrit is known as blood doping. Blood doping is beneficial in endurance athletes. Altitude acclimatization, which is considered an acceptable practice, yields improvements in performance similar to the banned practice of blood doping.

STIMULANTS

Caffeine

Caffeine is a central nervous system stimulant that causes a feeling of decreased fatigue and increases endurance performance (Chap. 63). These changes occur through several different mechanisms, including increased calcium permeability in the sarcoplasmic reticulum and enhanced contractility of muscle; phosphodiesterase inhibition and subsequent increased cyclic nucleotides; adenosine blockade leading to vasodilation; and inhibited lipolysis.

Amphetamines

The beneficial effects of amphetamines in sports result from their ability to mask fatigue and pain. Initial studies done in soldiers showed that they could march longer and ignore pain when taking amphetamines. Other studies show no significant effects on exercise performance (Chap. 73).

SODIUM BICARBONATE

Sodium bicarbonate loading, known as "soda loading," has a long history of use in horse racing. Sodium bicarbonate may buffer the lactic acidosis caused by exercise, thereby delaying fatigue and enhancing performance. Several studies demonstrated improved performance in running when sodium bicarbonate was ingested 2–3 hours before competition. Adverse effects of bicarbonate loading include diarrhea, abdominal pain, and the possibility of hypernatremia.

DIURETICS

Diuretics are used in sports in which the athlete must achieve a certain weight to compete in discrete weight classes. In addition to weight loss, body builders find that diuretic use gives greater definition to the physique as the skin draws tightly around the muscles. Diuretics also result in increased urine production, thereby diluting the urine and making it more difficult to detect other banned xenobiotics. Diuretic use can produce consequential fluid and electrolyte abnormalities (Chap. 60).

MISCELLANEOUS AGENTS

Chromium Picolinate

Chromium acts as a cofactor to enhance the action of insulin. It is found naturally in meats, grains, raisins, apples, and mushrooms. It is sold as chro-

mium picolinate because picolinic acid is thought to enhance chromium absorption. Studies do not demonstrate an increase in strength or changes in body composition or glucose metabolism when chromium is administered in a controlled fashion. Anemia may result from chromium picolinate doses greater than 200 μg/d.

LABORATORY DETECTION

Analysis of samples on the international level is performed by a limited number of accredited laboratories. The majority of tests are done on urine, with careful procedural requirements regarding handling of samples. Capillary gas chromatography is the most important technique currently used in laboratories. Gas chromatography is typically combined with mass spectrometry for detection of the majority of substances. Analysis of the urine by gas chromatography-mass spectrophotometry is the current standard for the detection of anabolic androgenic steroids. Detection of exogenously administered peptide hormones is difficult because of the structural similarity to the endogenous substance. Erythropoietin is directly measured by a monoclonal antierythropoietin antibody test, which does not distinguish between endogenously produced and exogenously administered recombinant erythropoietin. Consequently, indirect methods of detecting EPO use are employed, such as the measurement of the hemoglobin or hematocrit.

Masking Agents

Some agents are available for the sole purpose of interfering with urine testing. These agents are added to the urine. The list of prohibited masking agents includes diuretics, epitestosterone, probenecid, plasma expanders such as albumin, dextran, and hydroxymethyl starch, and α-reductase inhibitors such as finasteride and dutasteride. Probenecid blocks the urinary excretion of the glucuronide conjugates of AAS.

45 Food Poisoning

The most common causes of foodborne disease are bacteria—*Salmonella* spp, *Shigella* spp, *Clostridium perfringens, Staphylococcus aureus, Campylobacter* spp, *Bacillus cereus, Escherichia coli,* group A *Streptococcus, Clostridium botulinum, Vibrio cholera*; viruses—hepatitis A, E, F, and G, Norwalk virus; parasites—*Entamoeba histolytica, Giardia lamblia, Trichinella spiralis*; fishborne toxins—scombrotoxin, ciguatoxin, paralytic shellfish; chemicals—heavy metals, monosodium glutamate; and plants and mushrooms (Table 45–1).

FOODBORNE POISONING WITH NEUROLOGIC SYMPTOMS

The differential diagnosis of foodborne poisoning presenting with neurologic symptoms is vast (Tables 45–2 and 45–3). Knowing where the fish was caught is often helpful, but refrigerated transport of foods and rapid worldwide travel can complicate the assessment.

Ciguatera Poisoning

Ciguatera poisoning is one of the most commonly reported vertebrate fishborne poisonings, accounting for almost half of the reported cases in the United States. It is endemic to warm-water, bottom-dwelling shore reef fish living around the globe between 35° north and 35° south latitude. There are more than 500 fish species involved, with the barracuda, sea bass, parrot fish, red snapper, grouper, amber jack, kingfish, and sturgeon the most common sources. The common factor is the comparably large size of the fish involved.

Photosynthetic dinoflagellates, such as *Gambierdiscus toxicus,* and bacteria within the dinoflagellate are the origins of ciguatoxin. These dinoflagellates are the main nutritional source for small herbivorous fish; as these small fish are the major food source for larger carnivorous fish, the ciguatoxin becomes increasingly concentrated in the flesh, adipose tissue, and viscera of larger and larger fish.

Ciguatoxin does not harm the fish. The appearance, taste, and smell of the ciguatoxic fish are usually unremarkable. The majority of symptomatic episodes begin 2–6 hours after ingestion, 75% within 12 hours, and all but 4% within 24 hours. Symptoms include acute onset of diaphoresis; abdominal pain with cramps, nausea, vomiting, a profuse watery diarrhea; and a constellation of dramatic neurologic symptoms. Headaches are common. A sensation of loose, painful teeth may occur. Typically, peripheral dysesthesias and paresthesias predominate. Watery eyes, tingling, and numbness of the tongue, lips, throat, and perioral area also occur. A strange metallic taste is frequently reported. A reversal of temperature discrimination is reported, but the pathophysiology remains to be elucidated. Myalgias, most often in the lower extremities, arthralgias, ataxia, and weakness are commonly experienced. Bradycardia and orthostatic hypotension are also described. The GI symptoms usually subside within 24–48 hours; however, cardiovascular and neurologic symptoms may persist for several days to weeks, depending on the amount of toxin ingested.

TABLE 45–1. Epidemiology of Foodborne Poisoning Reported to the CDC (1993–1997)

Etiology	Cases	Outbreaks	Deaths
Salmonella	32,610	357	13
Escherichia coli[a]	3,260	84	8
Clostridium perfringens	2,772	57	0
Other parasitic	2,261	13	0
Other viral	2,104	24	0
Shigella	1,555	43	0
Staphylococcus aureus	1,413	42	1
Norwalk virus	1,233	9	0
Hepatitis A virus	729	23	0
Bacillus cereus	691	14	0
Other bacterial	609	6	1
Campylobacter	539	25	1
Scombrotoxin	297	69	0
Ciguatoxin	205	60	0
Streptococcus, group A	122	1	0
Listeria monocytogenes	100	3	2
Clostridium botulinum	56	13	1
Giardia lamblia	45	4	0
Vibrio parahaemolyticus	40	5	0
Other chemical	31	6	0
Yersinia enterocolitica	27	2	1
Mushroom poisoning	21	7	0
Brucella	19	1	0
Trichinella spiralis	19	2	0
Heavy metals	17	4	0
Streptococcus, other	6	1	0
Shellfish	3	1	0
Vibrio cholerae	2	1	0
Monosodium glutamate	2	1	0

[a]The fatality rate of *E. coli* 0157:H7 increased dramatically in the late1990s.

Laboratory analysis using an ELISA (enzyme-linked immunosorbent assay) test for ciguatera toxin can be performed; alternatively, HPLC (high-pressure liquid chromatography) is accurate. Initial treatment for victims of ciguatoxin poisoning include standard supportive care for a toxic ingestion. In most patients, elimination of the toxin is accelerated if vomiting (40%) and diarrhea (70%) have occurred. There may be some benefit from the administration of activated charcoal. IV mannitol may decrease neurologic and muscular dysfunctional symptoms associated with ciguatera. Mannitol should be used with caution, as it may cause hypotension.

Ciguateralike Poisoning

Moray, conger, and anguillid eels carry a ciguatoxinlike neurotoxin in their viscera, muscles, and gonads that does not affect the eel itself. Individuals who eat these eels may manifest neurotoxic symptomatology similar to that which occurs with ciguatoxin, or they may show signs of cholinergic toxicity, such as hypersalivation, nausea, vomiting, and diarrhea. Shortness of breath, mucosal erythema, and cutaneous eruptions may also occur. Management is supportive.

TABLE 45–2. Differential Diagnosis of Possible Foodborne Poisoning Associated with Neurologic Symptoms

Anticholinergic poisoning
Bacterial food poisoning
Bends type I, II, III (caisson disease)
Botulism
Carbon monoxide
Diphtheria
Eaton-Lambert syndrome
Encephalitis
Metals
Migraine
MSG (monosodium glutamate)
Myasthenia gravis
Organic phosphorous compounds
Plant ingestions (poison hemlock, buckthorn)
Poliomyelitis
Tick paralysis

Scombroid Poisoning

Scombroid poisoning was originally described with the Scombroidae fish (including the large, dark-meat marine tuna, albacore, bonito, mackerel, and skipjack). However, the most commonly ingested vectors are mahi mahi and amber jack. All of the implicated fish species live in temperate or tropical waters. This type of poisoning differs from other fishborne causes of illness in that it is entirely preventable if the fish is properly stored after it is removed from the water. The implicated fish all have a high concentration of histidine in their dark meat. *Morganella morganii, E. coli,* and *Klebsiella pneumoniae,* commonly found on the surface of the fish, contain a histidine decarboxylase enzyme that acts on a warm (not refrigerated), freshly killed fish to convert histidine to histamine, saurine, and other heat-stable substances. The appearance, taste, and smell of the fish is usually unremarkable. Rarely, the skin has an abnormal "honeycombing" character, or a pungent, peppery taste that may be a clue to its toxicity.

Usually, within minutes to hours after eating the fish, the individual experiences numbness, tingling, or a burning sensation of the mouth, dysphagia, headache, and, of particular significance for scombroid poisoning, a peculiar flush characterized by an intense diffuse erythema of the face, neck, and upper torso. The prognosis is good with appropriate supportive care and parenteral antihistamines such as diphenhydramine. H_2-receptor antagonists such as cimetidine or ranitidine may also be useful in alleviating symptoms. The patient may be reassured that he or she is not allergic to fish if other individuals experience a similar reaction to eating the same fish at the same time, or if any remaining fish can be preserved and tested for elevated levels of histamine.

Shellfish Poisoning

Molluscs ingest and filter large quantities of dinoflagellates. During the "non-R" months (May through August) in the northern hemisphere these dinoflagellates are responsible for the "red tides." The number of toxic dinoflagellates may be so overwhelming that birds and fish die, and humans who walk along the beach may suffer respiratory symptoms caused by aerosolized toxin.

TABLE 45–3. Common Foodborne Neurologic Diseases (Primary Presenting Symptoms)

	Onset/Duration*	Symptoms	Toxin Source/Toxin*/ Mechanism**	Diagnosis/Therapy*
Ciguatera	2–30 h *Months to years	t, p, n, v, d	Large reef fish: amber jack, barracuda, snapper, parrot, sea bass, moray (dinoflagellate, source) *Ciguatoxin **↑ sodium channel permeability	Clinical, mouse bioassay, immunoassay *Supportive, mannitol, amitriptyline
Tetrodotoxin	Minutes to hours *Days	p, r, ↓ bp n, v, d	Puffer fish, *fugu,* blue-ringed octopus, newts, horseshoe crab *Tetrodotoxin **Blocks sodium channel	*Clinical **Respiratory support
Neurotoxic shellfish poisoning	15 min to 18 h *Days	b, t, n, v, d, p	Mussels, clams, scallops, oysters, *P. brevis:* "red tide" *Brevetoxin ** ↑ Sodium channel permeability	Clinical, mouse bioassay of food, HPLC
Paralytic shellfish poisoning	30 min *Days	r, p, n, v, d	Mussels, clams, scallops, oysters, *P. catanella, P. tamarensis* *Saxitoxin **↓ sodium channel permeability	Clinical, mouse bioassay of food, HPLC *Respiratory support
Amnestic shellfish poisoning	15 min to 38 h *Years	a n, v, d, p, r	Mussels, possibly other shellfish; *N. pungens;* *Domoic acid **Glutamate analog	Clinical, mouse bioassay of food, HPLC *Respiratory support
Botulism	12–73 h	v, d, r, w	Home-canned foods, ? honey, corn syrups, *C. botulinum* *Botulinum toxin **Binds to presynapse, blocks acetylcholine release	Clinical immunoassay *Antitoxin, respiratory support

n = nausea; v = vomiting; d = diarrhea; p = paresthesias; r = respiratory depression; b = bronchospasm; t = temperature reversal sensation; a = amnesia; bp = hypotension; w = weakness; ↑ = increased; ↓ = decreased.

Ingestion of shellfish, including oysters, clams, mussels, and scallops, contaminated by dinoflagellates or algae may cause neurotoxic, paralytic, and amnestic syndromes. The dinoflagellates most frequently implicated are *Ptychodiscus brevis* (formerly *Gymnodinium breve*), the diatom causing neurotoxic shellfish poisoning; *Protogonyaulax catanella,* and *P. tamarensis*, which cause paralytic shellfish poisoning; and *Nitzschia pungens*, the diatom implicated in amnestic shellfish poisoning.

Paralytic shellfish poisoning (PSP) is caused by saxitoxin. Saxitoxin blocks the voltage-sensitive sodium channel in a manner identical to tetrodotoxin (see below). Symptoms usually occur within 30 minutes of ingestion. Neurologic symptoms predominate and include paresthesias and numbness of the mouth and extremities, a sensation of floating, headache, ataxia, vertigo, muscle weakness, paralysis, and cranial nerve dysfunction manifested by dysphagia, dysarthria, dysphonia, and transient blindness. Fatalities may occur as a result of respiratory failure, usually within the first 12 hours after symptom onset. Muscle weakness may persist for weeks. Treatment is supportive, but emphasizes early intervention for respiratory failure.

Neurotoxic shellfish poisoning (NSP), is caused by brevetoxin. Brevetoxin, produced by *P. brevis*, is a lipid-soluble, heat-stable polyether toxin similar to ciguatoxin. It acts by stimulating sodium flux through the sodium channels of both nerve and muscle. NSP is characterized by gastroenteritis with associated neurologic symptoms. Gastrointestinal symptoms include abdominal pain, nausea, vomiting, diarrhea, and rectal burning. Neurologic features include paresthesia, reversal of hot and cold temperature sensation, myalgia, vertigo, and ataxia. Other symptoms may include headache, malaise, tremor, dysphagia, bradycardia, decreased reflexes, and dilated pupils. Paralysis does not occur. The incubation period is 3 hours (range: 15 minutes to 18 hours). Duration of symptoms is on average 17 hours (range: 1–72 hours). Treatment is supportive and severe respiratory depression is very uncommon.

Amnestic shellfish poisoning (ASP) is caused by domoic acid. Domoic acid is a structural analog of glutamic and kainic acids produced by the diatom *Nitzschia pungens*. Amnestic shellfish poisoning is characterized by GI symptoms of nausea, vomiting, abdominal cramps, and diarrhea, and by neurologic symptoms of memory loss and, less frequently, coma, seizures, hemiparesis, ophthalmoplegia, purposeless chewing, and grimacing. The onset of symptoms after ingestion of mussels is 5 hours (range: 15 minutes to 38 hours). The mortality rate is 2%, with death most frequently occurring in older patients who suffer more severe neurologic symptoms. Ten percent of victims may suffer long-term antegrade memory deficits, as well as motor and sensory neuropathy.

Tetraodon Poisoning

This type of fish poisoning involves only the order *Tetraodontiformes*. Approximately 100 fresh and saltwater species of this order exist, including a number of pufferlike fish such as the globe fish, balloon fish, blowfish, and toad fish. Tetrodotoxin is also isolated from the blue-ringed octopus and the gastropod mollusc and has caused fatalities from ingestion of horseshoe crab eggs. In addition, certain tetrodotoxin-containing newts (*Taricha, Notophthalmus* [triturus], and *Cynops*), in particular the *Taricha granulosa*, found in Oregon, California, and southern Alaska, can be fatal when ingested.

Symptoms of tetraodon poisoning typically occur within minutes of ingestion. Headache, diaphoresis, dysesthesias, and paresthesias of the lips, tongue, mouth, face, fingers, and toes evolve rapidly. Buccal bullae and salivation may

develop. Dysphagia, dysarthria, nausea, vomiting, and abdominal pain may ensue. Generalized malaise, loss of coordination, weakness, fasciculations, and an ascending paralysis (with risk of respiratory paralysis) occur in 4–24 hours. Other cranial nerves may be involved. In more severe toxicity, hypotension is present. In some studies, mortality approached 50%. Therapy is supportive.

FOODBORNE POISONING ASSOCIATED WITH GASTROENTERITIS, ANEMIA, THROMBOCYTOPENIA, AND AZOTEMIA

This constellation of findings is typical for the hemolytic uremic syndrome (HUS), which is frequently caused by a bacterial gastroenteritis. The most common organism responsible is *E. coli* O157:H7. Laboratory findings typically include a microangiopathic hemolytic anemia, thrombocytopenia, and acute intrinsic renal failure. Other laboratory findings include hyperkalemia, metabolic acidosis, hyponatremia, and hypocalcemia. Liver aminotransferases may be elevated, and pancreatic involvement may produce hyperamylasemia, elevated lipase, and hyperglycemia. Treatment of HUS should focus on meticulous supportive care, with fluid and electrolyte balance being a priority. Peritoneal dialysis or hemodialysis should be instituted early for azotemia and for hyperkalemia, acidosis, or fluid overload.

FOODBORNE POISONING ASSOCIATED WITH DIARRHEA AND AN ELEVATED TEMPERATURE

The initial differential diagnosis for acute diarrhea involves several etiologies: infectious (bacterial, viral, parasitic, and fungal), structural (including surgical), metabolic, functional, toxin-induced, and food-induced. An elevated temperature may be caused by invasive organisms, including *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, invasive *E. coli, Vibrio parahaemolyticus*, and *Yersinia* spp, as well as some viruses. Episodes of acute gastroenteritis not associated with fever are usually caused by organisms producing toxins, including *S. aureus, B. cereus, C. perfringens,* enterotoxigenic *E. coli*, and viruses.

The timing of onset of diarrhea after exposure or the incubation period can be useful in differentiating its causes. Extremely short incubation periods of less than 6 hours are typical for *Staphylococcus*, *B. cereus* (type I), enterotoxigenic *E. coli*, and preformed enterotoxins, as well as roundworm larvae ingestions. Intermediate incubation periods of 8–24 hours are found with *C. perfringens*, *B. cereus* (type II enterotoxin), enteroinvasive *E. coli*, and *Salmonella* spp. Longer incubation periods are seen in other bacterial causes of acute gastroenteritis.

EPIDEMIOLOGY

Epidemiologic analysis is of immediate importance, particularly when GI diseases strike more than one person in a group. If available, an infectious disease consultant or infection control officer may be called for assistance. Alternatively, assistance from state and local health departments should be sought.

Staphylococcus Species

In cases of suspected food poisoning with a short incubation period, the physician should first assess the risk for staphylococcal causes. The usual foods associated with staphylococcal toxin production include milk products and other proteinaceous foods, cream-filled baked goods, potato and chicken sal-

ads, sausages, ham, tongue, and gravy. Patients with staphylococcal food poisoning rarely have a significant temperature elevation, although in a review of 2992 documented cases, 16% had a subjective sense of fever. Abdominal pain, nausea followed by vomiting, and diarrhea dominate the clinical findings. Diarrhea does not occur in the absence of nausea and vomiting. The mean incubation period is 4.4 hours with a mean duration of illness of 20 hours.

Salmonella Species

Salmonella enteritidis infections are a great concern in the United States. People who consume raw or undercooked eggs or raw milk are most at risk for salmonella enteritis. Household pets are also known to harbor *Salmonella* spp. Chicks, turtles, and iguanas carry salmonella and frequently transmit the organism to household contacts, including infants, who are at particular risk for invasive diseases.

Campylobacter jejuni

Campylobacter jejuni is commonly isolated in children younger than 5 years of age, and in adults 20–40 years of age. *Campylobacter* enteritis outbreaks are more common in the summer months in temperate climates. The most frequent sources of *Campylobacter* in food are raw or undercooked poultry products and unpasteurized milk.

The incubation period for *Campylobacter* enteritis varies from 1–7 days (mean: 3 days). Typical symptoms include diarrhea, abdominal cramps, and fever. Other symptoms may include headache, vomiting, excessive gas, and malaise. The diarrhea may contain gross blood, and frequently leukocytes are present on microscopic examination. Illness usually lasts 5–6 days (range: 1–8 days). Rarely, symptoms may last for several weeks. Severe presentations include lower GI hemorrhage, abdominal pain mimicking appendicitis, a typhoidlike syndrome, reactive arthritis, and meningitis. Treatment is supportive consisting of volume resuscitation, and can include quinolone antibiotics in more severe cases.

Yersinia enterocolitica

Yersinia enterocolitica causes enteritis that typically presents with fever, abdominal pain, and diarrhea, which usually contains mucus and blood. The incubation period may be 1 day to 1 week or more. Sources of human infection include milk products, raw pork products, infected household pets, and person-to-person transmission. Therapy is usually supportive; however, patients with invasive disease (eg, bacteremia, bacterial arthritis) should be treated with intravenous antibiotics. Fluoroquinolones and third-generation cephalosporins are highly bacteriocidal against *Yersinia* spp.

Listeria monocytogenes

Listeriosis transmitted by food usually occurs in pregnant women, their fetuses, the elderly, and immunocompromised individuals (corticosteroid use, malignancy, diabetes, renal disease, HIV infection). Typical food sources include unpasteurized milk, soft cheeses, and undercooked chicken. Treatment with intravenous ampicillin or trimethoprim-sulfamethoxazole is indicated for systemic listerial infections.

Intestinal Parasitic Infections

The popularity of eating raw fish, usually from Japanese restaurants, has led to an increase in reported intestinal parasitic infections. The etiologic agents are typically roundworms (*Eustrongylides, Anisakis*) or fish tapeworms (*Diphyllobothrium* spp). Symptoms of anisakiasis, or eustrongylidiasis, that are localized to the stomach typically occur 1–12 hours after eating raw fish, whereas symptoms of lower intestinal involvement may be delayed for days or weeks. Diagnosis is usually established on visual inspection of the larvae (on endoscopy, laparotomy, or pathologic examination), which are typically pink or red.

Monosodium Glutamate

The so-called Chinese restaurant syndrome is induced by ingestion of monosodium glutamate (L-sodium glutamate [MSG]). Individuals present with burning, facial pressure, headache, flushing, chest pain, GI symptoms usually limited to nausea and vomiting, and, infrequently, life-threatening bronchospasm and angioedema. Absorption is more rapid following fasting, and the typical burning symptoms rapidly spread over the back, neck, shoulders, abdomen, and, occasionally, the thighs. Gastrointestinal symptoms are rarely prominent. Symptoms can usually be prevented by prior ingestion of food. When symptoms do occur, they usually last approximately 1 hour.

FOOD POISONING AND BIOTERRORISM

The threat of terrorist assaults has received increased attention recently and is discussed elsewhere in this text (Chaps. 126 and 127). Food as a vehicle for intentional contamination with the intent of causing mass suffering or death has occurred in the United States. In the first report, 12 laboratory workers suffered gastrointestinal symptoms, primarily severe diarrhea, from consuming food served in the staff break room which had been purposefully contaminated with *Shigella dysenteriae* type 2. The second cases series describes a large community outbreak of food poisoning caused by *Salmonella typhimurium*. A total of 751 people suffered salmonella gastroenteritis. The outbreak was caused by intentional contamination of restaurant salad bars and coffee creamer by members of a religious commune using a culture of *S. typhimurium* purchased before the outbreak of food poisoning.

Reasons for the delay in identifying the outbreak as a purposeful food poisoning include (a) no apparent motive; (b) no claim of responsibility; (c) no pattern of unusual behavior in the restaurants; (d) no disgruntled restaurant employees identified; (e) epidemic exposure curves indicated multiple time points for contamination, suggesting a sustained source of contamination, not a single act; (f) no previous event of similar nature as a reference; (g) other possibilities seemed more likely (eg, repeated unintentional contamination by restaurant workers); and (h) fear that the publicity necessary to aid the investigation might generate copy cat criminal activity.

46 Botulism

The word *botulism* is derived from "botulus," the Latin word for sausage, because this classic foodborne poisoning was directly linked to inadequate preservation of varied forms of sausages more than 200 years ago. Clostridial species are ubiquitous, with bacteria and spores present in soil, seawater, and air. As such, botulism outbreaks can occur anywhere in the world. Approximately 1.25 cases of foodborne botulism per 10 million people occur annually in the United States and the etiologies of botulism are 72% infant, 24% foodborne, 3% wound, and 1% adult type. Approximately 70% of reported cases involved only 1 person, 20% involved 2 persons, and only 10% involved more than 2 persons (mean: 2.7 cases per outbreak). A current case fatality rate of 5.8% is reported.

CHARACTERISTICS OF *CLOSTRIDIUM BOTULINUM, CLOSTRIDIUM BUTYRICUM*, AND *CLOSTRIDIUM BARATII*

Clostridia are spore-forming, anaerobic, Gram-positive bacilli. The genus *Clostridium* consists of at least 4 variants that produce 7 neurotoxic proteins that cause human botulism: *C. botulinum*, which produces toxin types A, B and E; *C. baratii*, which produces toxin type F; *C. butyricum*, which also produces toxin type E and *C. argentinense*, which produces toxin type G. In the United States, toxin type A is found west of the Mississippi, toxin type B is found east of the Mississippi, particularly in the Allegheny range, and toxin type E is found in the Pacific Northwest. Toxin types A and B are typically found in poorly processed meats and vegetables, and toxin type E is commonly found in raw or fermented marine fish and mammals. Food contaminated with *C. botulinum* toxin types A and B often looks and smells abnormal and appears putrefied because of the action of proteolytic enzymes. In contrast, because toxin type E organisms are saccharolytic, not proteolytic, food contaminated with toxin type E may look and taste normal.

All botulinum spores are dormant and highly resistant to damage. They can withstand boiling at 212°F (100°C) for hours, although 30 minutes of moist heat at 248°F (120°C) usually destroys them. At high altitudes, where the boiling point of water may be as low as 202.5°F (94.7°C), a minimum of 30 minutes of boiling may be required to destroy the toxin. Factors that promote germination of spores in food are a pH greater than 4.5, a sodium chloride content less than 3.5%, or a low nitrite level. As opposed to the spores, the toxin itself is heat-labile and can be destroyed by heating to 176°F (80°C) for 30 minutes or to 212°F (100°C) for 10 minutes.

PATHOPHYSIOLOGY

The mouse LD_{50} (median lethal dose for 50% of test subjects) is 3 million molecules of toxin injected intraperitoneally. The human oral lethal dose is 1 μg/kg. Botulinum toxin binds to serotype specific receptors on the mucosal surfaces of gastric and small intestinal epithelial cells where endocytosis followed by transcytosis permits release of the toxin on the serosal cell surface. Release into the systemic circulation allows uptake into presynaptic acetylcholine containing neurons. Once inside the cell, the light chain of the toxin acts as a zinc-dependent endopeptidase to cleave polypeptides that are essen-

tial components of the neurotransmitter release apparatus (Figure 46–1). As a result, cholinergic transmission at all acetylcholine-dependent synapses in the peripheral nervous system is impaired. However, there is no effect on the central nervous system or axonal conduction.

SIGNS AND SYMPTOMS

Foodborne Botulism, Adult Type (In Vitro)

Foodborne botulism results from ingestion of food containing large amounts of toxin. Although the median incubation period for all patients is 1 day, it ranges from 0–7 days for toxin type A, 0–5 days for toxin type B, and 0–2 days for toxin type E. The initial phase of the disease is often so subtle as to go unnoticed. Early gastrointestinal signs and symptoms include nausea, vomiting, abdominal distension, and pain. There may or may not be a time lag (from 12 hours to several days, but typically not more than 24 hours) before one or more of the following signs and symptoms appear: constipation, dry or sore mouth and throat, dysphonia (typically manifested by a nasal quality to the voice), dysarthria, dysphagia (at times predominant and severe); blurred vision with impaired accommodation, diplopia, descending, bilaterally symmetric motor paralysis beginning with abducens (VI) or oculomotor (III) nerve palsy (frequently resulting in strabismus); mydriasis (often fixed); respiratory insufficiency; and urinary retention. The mental status and remainder of the neurologic examination remain normal.

The Centers for Disease Control and Prevention (CDC) case definition is established when diplopia, blurred vision, bulbar weakness, and symmetric paralysis are present and:

- Botulinum toxin is detected in serum, stool, or implicated food samples, or
- *C. botulinum* is isolated from stool, or
- A clinically compatible case occurs when an individual is epidemiologically linked to a laboratory-confirmed case of botulism.

Lateral rectus palsy (VI), ptosis, and sluggish pupillary reactivity are indicative of impending respiratory insufficiency. As weakness progresses, deep-tendon reflexes may diminish. The pulse is frequently normal or slow, and temperature in adults typically remains normal.

The most difficult and frequently encountered problem is differentiating between botulism and the Miller Fisher variant of the Guillain-Barré syndrome.

Infant Botulism (In Vivo Infant Intestinal Colonization)

Infants lack the ability to kill ingested bacteria, which slowly liberate toxin. Because the toxin in infant botulism is absorbed gradually as it is produced, the onset of clinical manifestations may be less abrupt than in cases of foodborne botulism. Affected children are always younger than 1 year of age (usually 1–3 months) and characteristically have normal gestations and births. The first signs of infant botulism are constipation; difficulty with feeding, sucking, and swallowing; feeble crying; and a "floppy" baby with diffuse, decreased muscle tone. This decreased muscle tone is particularly apparent in the limbs and neck. Ophthalmoplegia, loss of facial grimacing, dysphagia, diminished gag reflex, poor anal sphincter tone, and respiratory failure are also present, but fever and enteric symptoms do not occur. The differential diagnosis of infant botulism initially includes dehydration, failure to thrive, hypotonia, sepsis, or a viral syndrome.

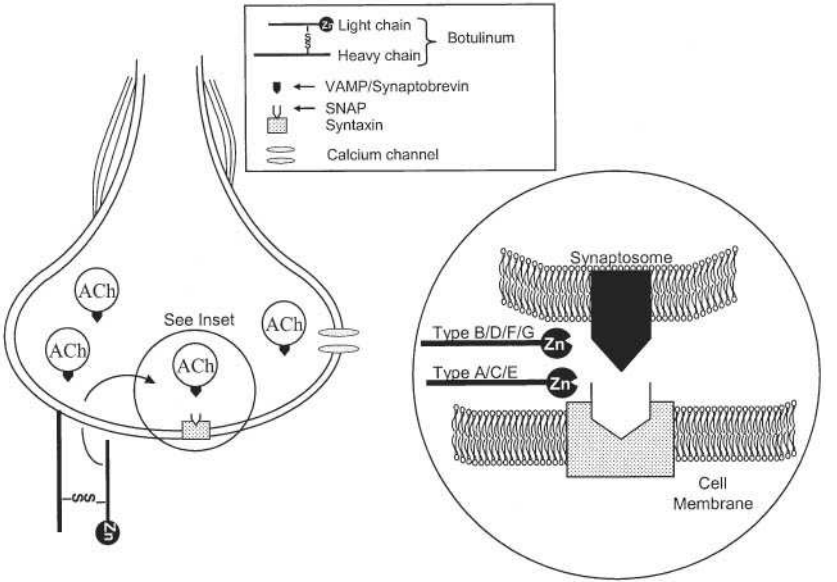

FIG. 46–1. Botulinum toxin consists of two peptides linked by disulfide bonds. The heavy chain is responsible for specific binding to acetylcholine (ACh)-containing neurons. Following binding to the cell surface, the entire complex undergoes endocytosis and subsequent translocation of the light chain into the nerve cell cytoplasm. The light chain contains a zinc-requiring endopeptidase that cleaves proteins required by the docking–fusion complex critical to neuroexocytosis. Botulinum toxin type B targets both vesicle-associated membrane protein (VAMP)/synaptobrevin, a docking protein located on the ACh-containing synaptic vesicles (synaptosome). Botulinum toxins types A and E proteolyse synaptosomal-associated protein (SNAP), a component of the presynaptic cell-membrane docking complex (associated with syntaxin). After these important components of the docking complex are destroyed, neurotransmitter release cannot proceed, resulting in clinical findings consistent with acetylcholine deficiency.

Wound Botulism (In Vivo)

The "classic" presentation of wound botulism is a patient injured in a motor vehicle crash who sustains a deep muscle laceration, crush injury, or compound fracture treated with open reduction. The wound is typically quite dirty and usually associated with inadequate débridement, subsequent purulent drainage, and local tenderness, although in other cases, the wound may appear unremarkable. Four to 18 days later, cranial nerve palsies and the other neurologic findings typical of botulism may appear. Fever may be prominent and associated with the tissue infection presumed to harbor the clostridial organisms. Typical gastrointestinal signs of food-related botulism are usually absent.

Most of the recent cases of wound botulism reported are associated with the subcutaneous injection of heroin.

Adult Infectious Botulism (In Vivo Adult Intestinal Colonization)

Adult intestinal colonization may represent a variant form of infant botulism where gastrointestinal disease has produced an environment in which bacteria can survive and multiply. The incubation may be very prolonged and symptoms characteristic of botulism develop slowly.

Therapeutic and Inadvertent Botulism (In Vitro)

Currently, doses ranging between 10 and 100 ng of botulinum toxin type A (Botox or Dysport [available in Europe]) or botulinum toxin type B (Myobloc) are used therapeutically to treat facial nerve disorders and to eliminate frown lines, achalasia, dysphagia, dystonia, torticollis, axillary hyperhidrosis, migraine headaches, obesity, spasticity, voice and speech disorders (spasmodic dysphonia), and chronic anal fissures. The affected muscles then weaken by atrophy over a 3-week period, but recover within 2–4 months as nerve transmission is restored through sprouting of new nerve endings and functional connections at motor endplates.

Injected botulinum toxin diffuses into local tissues and adverse effects typically occur locally. Systemic manifestations are of concern when an inadvertent, excessive, or misdirected dose of toxin is administered. Even appropriately injected doses result in neuromuscular junction abnormalities throughout the body, infrequently producing autonomic dysfunction without muscle weakness.

DIAGNOSIS

Routine laboratory studies, including cerebrospinal fluid (CSF) analysis, are normal in patients with botulism, but help exclude other common etiologies for neuromuscular dysfunction. Specific tests that are particularly helpful in diagnosing botulism include the following.

Tensilon Test

Edrophonium (Tensilon) is a rapidly acting anticholinesterase used to diagnose myasthenia gravis and to differentiate myasthenia gravis from botulism. This drug prevents released acetylcholine from being metabolized, permitting continued reaction with postsynaptic receptors. An intravenous (IV) injection of 10 mg is prepared and then 1–2 mg is administered slowly, to avoid the nausea and vomiting commonly associated with larger doses. The remainder of the edrophonium is then given over the next 5 minutes. The strength of pa-

tients who have myasthenia gravis, but not botulism, will dramatically improve within 30–60 seconds, and this improvement will last 3–5 minutes.

Electromyography

The electromyography (EMG) pattern in all forms of botulism is characterized by brief, small, abundant motor unit action potentials (BSAPs, or low-amplitude, short-duration potentials). Motor nerve conduction velocity remains normal, because axon conduction is unaffected. Normal sensory nerve amplitudes and latencies are found.

Laboratory Testing

Samples of serum, stool, vomitus, gastric contents, and suspected foods should be subjected to anaerobic culture (*C. botulinum*) and toxin mouse bioassay (botulinum toxins). Although polymerase chain reaction studies can determine the presence of *C. botulinum* in food, this test is not yet available to determine the presence of *C. botulinum* in human specimens. Stool, serum, or suspected food samples can be used for a mouse neutralization bioassay. The materials are injected into the mouse peritoneum and subsequent paralysis and death of the mouse are considered to be a positive test. Control animals receive portions of the specimen materials that have been boiled to destroy the toxin or previously incubated with individual antitoxins to achieve neutralization and identification of toxin type.

TREATMENT

Supportive Care

Hospital admission is required for all patients with suspected botulism. Respiratory compromise is the usual cause of death from botulism. Careful continuous monitoring of respiratory status by assessing vital capacity, peak expiratory flow rate (PEFR), negative inspiratory force (NIF), pulse oximetry, and the presence or absence of a gag reflex is essential to determine the need for intubation as the patient begins to manifest signs of bulbar paralysis. The most reliable, readily obtainable test is the NIF, which can be used in most institutions to determine the need for intubation.

Gastric Decontamination

Gastric lavage or emesis should be initiated only for an asymptomatic person who very recently ingested a known contaminated food. An attempt should be made to remove the spores and toxin from the gut. Activated charcoal (1 g/kg) should be given as it adsorbs *C. botulinum* type A toxin in vitro and probably the other botulinum toxin types. If a cathartic is chosen, sorbitol is the preferable agent, as other agents, such as magnesium salts, can exacerbate neuromuscular blockade.

Wound Care

Thorough wound débridement is the most critical aspect of the management of wound botulism and should be performed promptly. Antibiotic therapy alone is inadequate, as there are several case reports of disease despite antibiotic therapy. Aminoglycoside antibiotics and clindamycin should not be used as they may exacerbate neuromuscular blockade.

Botulinum Antitoxin

Botulinum antitoxins types AB (bivalent) and ABE (trivalent) are available. Patients who receive antitoxin have a lower fatality rate and a shorter course of illness. Although antitoxin can prevent paralysis it does not affect already paralyzed muscles. To be most effective, therefore, antitoxin must be given as soon as possible.

An entire 10-mL vial of trivalent antitoxin should be given intravenously as a 1:10 vol/vol dilution in 0.9% sodium chloride solution over several minutes. If epidemiologic investigation identifies the organism, subsequent type-specific antitoxin therapy may be instituted if available. Because antitoxin is an equine globulin preparation, adverse reactions are common. The overall rate of adverse reactions including hypersensitivity and serum sickness is 9–17%, with an incidence of anaphylaxis as high as 1.9%. Epinephrine should always be readily available.

Penicillin

Penicillin G is one of many drugs with excellent in vitro efficacy against *C. botulinum* and is useful for wound management. However, penicillin has no role in the management of botulism caused by preformed toxin, nor has it been shown to prevent gut spores from germinating. For these reasons penicillin is not considered useful in infant and adult infectious botulism nor is it considered adequate for wound botulism.

Epidemiologic and Therapeutic Assistance

Whenever botulism is suspected or proven, the local health department should be called. The health department should report to the CDC 24-hour Emergency Operations Center at 770-488-7100. The CDC can provide or facilitate diagnostic, consultative, and laboratory testing services, access to bivalent or trivalent botulinum antitoxin, botulinum immunoglobulin, and assistance in epidemiologic investigations.

Botulinum Antitoxin

EQUINE IMMUNOGLOBULINS

Bivalent (serotypes A and B) and trivalent (serotypes A, B, and E) botulinum antitoxin are the available equine immunoglobulin preparations in the United States. The bivalent (AB) preparation is typically used for patients with presumed wound botulism, whereas the trivalent product is reserved for patients with foodborne botulism.

Botulinum antitoxin is distributed from the 9 regional centers of the Centers for Disease Control and Prevention (CDC) on a named patient basis after a probable diagnosis of botulism is established. The CDC Emergency Operations Center can be reached at 770-488-7100. Each 10-mL vial of the currently available trivalent botulinum antitoxin contains 7500 IU (2381 US units) of type A botulinum antitoxin, 5500 IU (1839 US units) of type B antitoxin, and 8500 IU (8500 US units) of type E antitoxin.

Currently there are only limited data available on the pharmacokinetics of antitoxin. Peak serum concentrations are 10–1000 times higher than the concentrations calculated to achieve toxin neutralization. Patients who received antitoxin within the first 24 hours after exposure have a shorter clinical course of botulism without regression of symptoms, but a comparable mortality rate to those who received antitoxin later. However, because the goal of antitoxin therapy is to halt the progression of botulism, there is little benefit to antitoxin administration once respiratory compromise has occurred.

In the presence of disease, 1 vial of the antitoxin is administered slowly IV over several minutes as a 1:10 vol/vol dilution in 0.9% sodium chloride solution. Subsequent doses may be given IV every 2–4 hours, if clinical progression of disease continues.

Like many other heterologous proteins, administration of this horse serum-derived preparation results in substantial adverse effects. The overall rate of anaphylaxis is reported to be as high as 1.9%. Because of the lethality of botulinum toxin, the risk of adverse drug reaction for the antitoxin is considered acceptable for anyone with presumed illness, as well as for anyone potentially exposed to the toxin. Pregnancy is not a contraindication to antitoxin administration and antitoxin has been used successfully in these circumstances.

Anaphylaxis should be anticipated, and the clinician should be prepared to treat this complication immediately with epinephrine. The smaller quantities of antitoxin used for botulism present a far smaller risk for serum sickness than do the larger amounts of equine antivenom previously used to treat snake envenomation. The risk of serum sickness from the refined serum proteins in botulinum antitoxin is approximately 4–10%.

HUMAN IMMUNOGLOBULINS

Human-derived preparations offer distinct advantages over equine-derived products in that they have a lower risk of anaphylaxis and do not sensitize the host to equine serum. A human-derived type E antitoxin was developed as 5000 IU per 2-mL vials for intramuscular use and was dosed between 1000 and 5000 IU based on the estimated quantity of toxin ingested for 100 Egyp-

tians who presumably had ingested botulinum toxin-contaminated uneviscerated salted mullet fish. The safety of the human-derived preparation allowed for repetitive dosing in any individual if clinical findings developed.

Human-derived botulism immune globulin (BIG-IV) was developed for use in the treatment of infant botulism. This pentavalent (types A, B, C, D, and E) immune globulin is harvested by plasmapheresis from human donors who received multiple immunizations with pentavalent botulinum toxoid. This product has a longer biologic half-life producing a prolonged effective period which is desirable in the infant form of botulism, where toxin is slowly and continuously produced in the intestine and absorbed. Results of the orphan-drug infant botulism prevention clinical trial of the human BIG-IV suggest many advantages over the current equine antitoxin therapy. In a randomized double-blind placebo controlled trial, BIG-IV reduced the mean length of hospital stay, the mean duration of intensive care stay, the mean duration of mechanical ventilation, the mean duration of tube or intravenous feeding, and the mean hospital charges in the 122 infants studies. Additionally, there were no serious adverse events.

BIG-IV is available through the CDC's Infant Botulism Treatment and Prevention Program (510-231-7600).

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47 Anticonvulsants

HISTORY AND EPIDEMIOLOGY

The search for nonsedating anticonvulsants to replace phenobarbital led to the introduction of phenytoin in 1938. After 1965, benzodiazepines, carbamazepine, and valproic acid were introduced, and widely gained use as anticonvulsants. These remained the only available agents until the most recent decade when the following anticonvulsants received approval for clinical use: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, felbamate, and vigabatrin. Anticonvulsants are also currently used in the treatment of mood disorders, refractory pain syndromes such as trigeminal neuralgia, bruxism, migraine headaches, drug withdrawal syndromes, and social phobias.

PHARMACOLOGY

Seizures result from 1 of 4 cellular mechanisms: sustained repeated firing of the sodium channels, excessive calcium conductance, increased excitatory neurotransmission (eg glutamic acid), or loss of control maintained by inhibitory neurotransmitters (eg γ-aminobutyric acid [GABA]). Correspondingly, the mechanisms of action of anticonvulsant drugs fall into 1 of 4 major categories: sodium channel inhibition, calcium channel inhibition, inhibition of excitatory amines, and GABA agonism. Frequently, more than one mechanism accounts for a drug's anticonvulsive action (Fig. 47–1).

PHENYTOIN/FOSPHENYTOIN

Because phenytoin is nonsedating in therapeutic doses, it is often preferred over the GABAergic anticonvulsants for the long-term management of epilepsy. Fosphenytoin, a water-soluble phenytoin derivative introduced in 1997, was developed to address the apparent shortcomings of parenteral phenytoin, such as its poor solubility and unsuitability for intramuscular injection.

Pharmacokinetics and Toxicokinetics

In very large oral overdoses, gastrointestinal absorption can be delayed up to several days. Phenytoin is extensively bound to serum proteins, mainly albumin. Only the unbound free fraction can cross biologic membranes and exert pharmacologic action. The major phenytoin metabolite, an arene oxide, is inactive but is believed to be responsible for the hypersensitivity reaction associated with the administration of phenytoin. Phenytoin follows Michaelis-Menten model of saturable enzyme kinetics and its apparent half-life of elimination is progressively prolonged as the plasma concentration increases (Chap. 9).

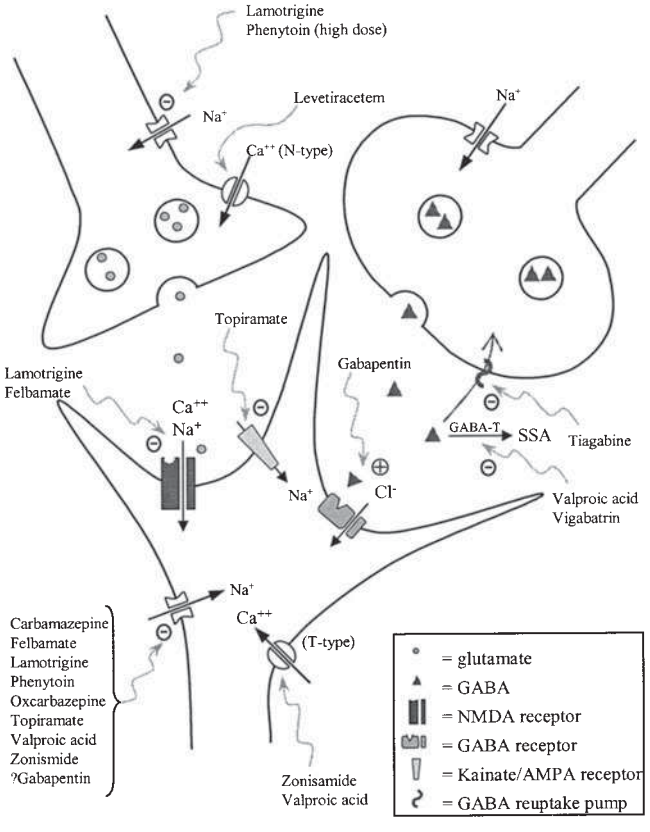

FIG. 47–1. Mechanism of action of anticonvulsants. SSA = succinic acid semialdehyde; GABA-T = GABA-transaminase.

Fosphenytoin (1.5 mg fosphenytoin = 1 mg phenytoin) is a water-soluble phosphate ester prodrug of phenytoin that is converted entirely to phenytoin by circulating phosphatases within 6–16 minutes of intravenous injection.

Clinical Manifestations

Acute phenytoin toxicity produces predominantly neurologic dysfunction that typically affects the cerebellar and vestibular systems. Phenytoin concentrations greater than 15 mg/L are typically associated with nystagmus, concentrations greater than 30 mg/L are associated with ataxia, and concentrations exceeding 50 mg/L are associated with lethargy, slurred speech, and pyramidal and extrapyramidal manifestations. There is no reported cardiotoxicity resulting from oral overdoses of phenytoin. Intravenous phenytoin, however, impairs myocardial contractility, decreases peripheral vascular resistance, and depresses myocardial conduction. These effects can be partially ascribed to the diluents used in the intravenous preparation of phenytoin: propylene glycol (40%) and ethanol (10%).

Intravenous phenytoin is commonly associated with local irritation. Extravasation may lead to local skin necrosis, possibly necessitating surgical intervention.

Diagnostic Testing

Serum phenytoin concentrations should be performed in all suspected cases of phenytoin toxicity. Because of unpredictable absorption, phenytoin concentrations should be repeated. Patients with impaired or decreased albumin-binding capacity can develop symptoms at total phenytoin concentrations within the therapeutic range. Determination of the free phenytoin fraction is helpful because it compares more reliably with the cerebrospinal fluid (CSF) concentrations than does the total phenytoin concentration.

Management

The treatment of patients with acute or chronic phenytoin overdoses remains largely supportive and phenytoin-related deaths are rare, even after massive overdoses. Aggressive use of activated charcoal with lowering of the phenytoin serum concentration may be harmful to the epileptic patient and multiple-dose activated charcoal (MDAC) should be used cautiously in these patients.

Healthy patients admitted to the hospital after oral phenytoin overdoses do not need routine cardiac monitoring because they do not experience dysrhythmias or cardiovascular complications.

Chapter 52 discusses the management of extravasation.

CARBAMAZEPINE/OXCARBAZEPINE

Pharmacokinetics and Toxicokinetics

Carbamazepine is lipophilic with slow and unpredictable absorption following oral administration and rapid distribution to all tissues. Concentrations may take up to 24 hours to reach a peak, especially following a large overdose or overdose of sustained-release preparations. Carbamazepine is metabolized primarily by cytochrome P450 (CYP) 3A4 to carbamazepine 10,11-epoxide which is pharmacologically active.

Oxcarbazepine is rapidly converted to the pharmacologically active 10-monohydroxy-10-oxocarbazepine metabolite before conjugation and renal elimination.

Clinical Manifestations

Acute carbamazepine toxicity is manifest by neurologic signs and symptoms in association with cardiovascular effects. The initial neurologic disturbances include nystagmus, ataxia, and dysarthria. In patients with a large overdose, fluctuations in level of consciousness are commonly followed by coma. Carbamazepine toxicity may cause seizures in nonepileptic patients, as well as in patients with underlying epilepsy. Cardiovascular effects include sinus tachycardia, hypotension with myocardial depression, and cardiac conduction abnormalities.

Diagnostic Testing

A serum carbamazepine concentration should be performed in all cases of suspected carbamazepine toxicity. Because of erratic absorption, the concen-

trations should be repeated every 4–6 hours and closely monitored until a downward trend is observed.

Oxcarbazepine will be detected on the carbamazepine assay and concentrations will be in the order of 1–3 mg/L.

Management

Multiple-dose activated charcoal has a therapeutic role in the management of patients with carbamazepine overdose, and is particularly helpful by reducing enterohepatic circulation. Concretions of carbamazepine should be suspected when plasma concentrations rise or the occurrence of symptoms is delayed. Cardiac monitoring for occurrence of QRS or QTc abnormalities is recommended. Although not formally studied, sodium bicarbonate should be administered if the QRS duration exceeds 100 msec. Carbamazepine-induced seizures usually respond to benzodiazepines.

VALPROIC ACID

Valproic acid (di-*n*-propylacetic acid [VPA]), a simple branched-chain carboxylic acid, is used to treat a broad spectrum of seizure disorders from simple and complex absence seizures to complex partial and myoclonic seizures. Valproic acid inhibits voltage-gated sodium channels and inhibits GABA transaminase.

Pharmacokinetic, Toxicokinetics, and Pathophysiology

Peak concentrations are usually reached in 6 hours except for enteric-coated and extended-release preparations, where peaks are delayed for up to 24 hours. VPA is 90% protein-bound at therapeutic concentrations, but this percentage decreases as the VPA concentration increases (Table 47–1).

Clinical Manifestations

Overdoses of VPA result in symptoms varying from lethargy to coma associated with cerebral edema. Nystagmus, ataxia, and tremor do not typically occur. The neurotoxicity is often less severe in the setting of acute overdose than in a patient chronically using valproic acid. Metabolic complications following acute valproic acid overdoses include hypernatremia, hypocalcemia, metabolic acidosis, hypocarnitinemia, and hyperammonemia. Metabolic acidosis may occur following massive overdoses and is a poor prognostic sign.

Pancreatitis, hepatotoxicity, and renal insufficiency are rare manifestations of acute toxicity. Chronic valproic acid therapy may lead to hepatotoxicity because of an aberration in fatty acid metabolism rather than a hypersensitivity reaction.

Diagnostic Testing

Serum valproic acid concentrations should be performed in all cases of valproic acid exposure. The concentrations should be repeated every 4–6 hours and closely monitored until a downward trend is observed. Electrolytes, blood gases, serum lactate, and serum ammonia concentrations should be monitored in all the patients. Hyperammonemia (>80 μg/dL or >35 mmol/L) occurs in 16–52% of patients on chronic VPA therapy.

TABLE 47–1. Pharmacokinetics of Anticonvulsants[a]

	Time to Peak Plasma Concentration[a] (h)	Therapeutic Serum Concentrations (mg/L)	Vd (L/kg)	Plasma Protein Binding (%)	Urinary Elimination Unchanged (%)	Active Metabolites	Apparent Plasma Elimination Half-Life (h)
Carbamazepine	3–24 in overdose	4–12	0.8–1.8	75	1	CBZ 10,11-epoxide	6–20 overdose 4.9–11.5 chronic
Felbamate	4	30–50	0.75	25	40	None	20–23
Gabapentin	3	2.7–4	0.8	0	100	None	5–7
Lamotrigine	2.5	4–18	1.2	55	10	None	14–50
Levetiracetam	1–2	10–70	0.7	10	66	None	5–8
Phenytoin	5–24 in overdose	10–20	0.6	>90	<5	None	6–60
Tiagabine	1–2	5–70 ng/mL	1	96	<5	None	5–9
Topiramate	1–4	4.5–30	0.5–0.8	15	60	None	20–30
Valproic acid	1–24 in overdose	50–120	0.1–0.2	>90	<5	2-en-VPA 3-OH-VPA 3-keto VPA	6–18
Vigabatrin	4	20–80	0.8	0	100	None	4–8
Zonisamide	4–6	6.7–40	1.2	40–60	<5	None	60

[a]After therapeutic oral administration, unless otherwise stated.

Management

Supportive management is all that is required to ensure complete recovery in most patients with VPA overdoses. Multiple-dose activated charcoal reduces the half-life of valproic acid from a mean of 12 hours to 4.8 hours and is recommended in patients in instances where serum concentrations are continuously rising. Carnitine should be administered if there is evidence of hyperammonemia or hepatotoxicity. For critically ill patients the loading dose is 100 mg/kg IV over 30 minutes (maximum 6 g) followed by 15 mg/kg IV over 10–30 minutes every 4 hours until clinical improvement occurs (see Antidotes in Brief: L-Carnitine). Hemodialysis increases clearance of valproic acid but should be reserved for patients with rapid deterioration, evidence of hepatic dysfunction, apparent continued absorption of VPA, and/or serum VPA concentrations in excess of 1000 mg/L.

GABAPENTIN

Gabapentin is a cyclohexane derivative of GABA.

Clinical Manifestations

Sedation, ataxia, slurred speech, and gastrointestinal symptoms are observed following acute gabapentin overdose. Clinical findings generally develop in under 5 hours and resolve within 4–24 hours.

Diagnostic Testing

Gabapentin testing is not routinely available for clinical use, and the therapeutic range is continuously evolving.

Management

The treatment of patients with gabapentin overdose is largely supportive. Activated charcoal may be useful to limit absorption. Despite a case report suggesting a role, flumazenil is not recommended in the management of gabapentin overdose.

LAMOTRIGINE

Clinical Manifestations

Neurologic manifestations such as lethargy, ataxia, nystagmus, and gastrointestinal symptoms are described following lamotrigine overdose. Coma, seizures, and cardiac conduction disturbances (QRS prolongation) may occur. Chronic overdoses of lamotrigine result in multiorgan involvement, including rashes, elevation in hepatic aminotransferases, rhabdomyolysis, and elevation of serum creatinine phosphokinase. It is unclear if this represents the anticonvulsant hypersensitivity syndrome etiologically. All abnormalities typically resolve upon withdrawal of the drug.

Diagnostic Testing

Lamotrigine concentrations are not available in a clinically relevant time frame.

Management

Supportive care and ECG monitoring are recommended. Lamotrigine-induced seizures should be treated with benzodiazepines.

TOPIRAMATE

Clinical Manifestations

Lethargy, ataxia, nystagmus, myoclonus, coma, seizures, and status epilepticus are reported following topiramate overdose. Echolalia and repetitive mouthing are reported. Nonanion gap metabolic acidosis as a result of inhibition of renal cortical carbonic anhydrase may be present, usually with high normal or elevated serum chloride, as well as hypokalemia (2.0–3.2 mEq/L). The metabolic acidosis appears within hours of ingestion and can persist for days.

Diagnostic Testing

Topiramate concentrations are not available in a clinically relevant time frame.

Management

Supportive care and activated charcoal are recommended as needed. Severe hyperchloremic metabolic acidosis should be treated with sodium bicarbonate 1–2 mEq/kg intravenously. Hemodialysis is generally recommended in patients who overdose on topiramate and have associated neurologic impairment, electrolyte abnormalities that have failed to respond to conventional therapy, or renal insufficiency.

TIAGABINE

Clinical Manifestations

Lethargy, facial myoclonus (grimacing), nystagmus, and posturing are described in patients who overdose on tiagabine. At very high plasma concentrations, seizures and status epilepticus may occur.

Diagnostic Testing

Tiagabine concentrations are not available in a clinically relevant time frame.

Management

Activated charcoal and supportive care are recommended. Seizures respond to administration of benzodiazepines and refractory status epilepticus should be treated with barbiturates.

LEVETIRACETAM

Clinical Manifestations

Levetiracetam overdose causes lethargy, coma, and possibly respiratory depression. Nystagmus is absent. Findings may persist for 24 hours.

Diagnostic Testing

Levetiracetam concentrations are not available in a clinically relevant time frame.

Management

Activated charcoal should be administered. Supportive care is recommended.

OTHER ANTICONVULSANTS

Vigabatrin

Agitation, coma, and long-term psychosis are reported after acute ingestion. Chronic toxicity can result in psychosis, dizziness, and tremor, which is usually mild and transient, as well as depression and psychosis. The treatment is largely supportive.

Felbamate

Mild lethargy and gastrointestinal symptoms, as well as crystalluria and reversible renal failure, are reported following acute overdose. The treatment of felbamate overdose is largely supportive.

Zonisamide

Overdose experience with zonisamide is limited. In therapeutic doses, zonisamide causes oligohidrosis and fever in children.

ANTICONVULSANT HYPERSENSITIVITY SYNDROME

Ill-defined since it was first described in 1950, the anticonvulsant hypersensitivity syndrome (AHS) is a disorder that occurs in approximately 1 of every 1000 to 10,000 exposures to anticonvulsants. Anticonvulsant hypersensitivity syndrome is traditionally associated with exposures to aromatic anticonvulsants such as phenytoin, carbamazepine, oxcarbazepine, phenobarbital, and primidone. Recent literature supports the inclusion of the nonaromatic lamotrigine as a causative agent. The anticonvulsant hypersensitivity syndrome occurs most frequently within the first 2 months of therapy and is not related to dose or serum concentration. The pathophysiology of AHS is related to the accumulation caused by insufficient detoxification by the enzyme epoxide hydrolase of arene oxide metabolites of the aromatic anticonvulsants.

The anticonvulsant hypersensitivity syndrome is defined by a triad of fever, rash, and internal organ involvement. The initial symptoms include fever, malaise, and pharyngitis (including tonsillitis). A skin eruption characterized by macular erythema evolves into a pruritic and confluent papular rash primarily involving the face, trunk, and, later, the extremities. Severely affected cases develop toxic epidermal necrolysis. Multiorgan involvement usually occurs 1–2 weeks into the syndrome. The liver is the most frequently affected organ, although involvement of the CNS (encephalitis), cardiac muscle (myocarditis), lungs (pneumonitis), renal system (nephritis), and thyroid (hyperthyroid thyroiditis followed by hypothyroidism) are rare but possible.

Prompt discontinuation of the offending anticonvulsant is essential to prevent symptom progression. Patients should be admitted to the hospital and receive methylprednisolone 0.5–1 mg/kg/d divided in 4 doses.

L-Carnitine

L-Carnitine (levocarnitine), an amino acid that is vital to mitochondrial use of fatty acids, is an orphan drug approved by the FDA for the treatment of L-carnitine deficiency secondary to valproic acid toxicity, caused by inborn errors of metabolism, associated with hemodialysis, and for zidovudine (AZT)-induced mitochondrial myopathy and pediatric cardiomyopathy. Although carnitine can exist as either the D or L form, only the L isomer is found endogenously, is active, and should be used therapeutically.

BIOCHEMICAL BASIS

Fatty acids provide 9 kcal/g and are an important source of energy for the body. The utilization of fatty acids requires L-carnitine–mediated passage through both the outer and inner mitochondrial membranes to reach the mitochondrial matrix where β-oxidation occurs. Enzymes in the outer and inner mitochondrial membranes (carnitine palmitoyltransferase and carnitine acylcarnitine translocase) catalyze the synthesis, translocation, and regeneration of L-carnitine.

L-CARNITINE HOMEOSTASIS

Approximately 54–87% of endogenous L-carnitine is derived from the diet, while the remainder is synthesized. Meat and dairy are the primary dietary sources, and although most plants supply very little, avocado and fermented soy products are exceptionally rich in this amino acid. The remainder of the carnitine needed by the body is synthesized.

PHARMACOKINETICS OF EXOGENOUS L-CARNITINE

L-carnitine is not bound to plasma proteins. The volume of distribution is 0.7 L/kg and the terminal elimination half-life averages 10–23 hours. Baseline plasma values for L-carnitine are 40 μmol/L but increase to 1600 μmol/L following administration of 40 mg/kg IV. Whereas 2 g administered IV produces a peak plasma concentration of 1000 μmol/L, oral administration of 2 g only produces peaks of 15–70 μmol/L. The time to peak concentrations following oral administration occurs at 2.5–7 hours, indicating a slow uptake by intestinal mucosal cells.

VALPROIC ACID AND HYPERAMMONEMIA

Valproic acid can cause hyperammonemia with or without symptoms and with or without hepatic dysfunction, which may occur either with therapeutic dosing or following an acute overdose. In the absence of hepatic dysfunction, the postulated mechanisms for hyperammonemia are unclear, but may be a result of an interference with the hepatic synthesis of urea or a small increase in the production of ammonia by the kidney.

Valproic acid induces both carnitine and acetyl-coenzyme A (acetyl-CoA) deficiencies by combining with L-carnitine as valproylcarnitine and with acetyl CoA as valproyl-CoA. Ultimately, the β-oxidation of all fatty acids is

reduced, decreasing energy production. Valproic acid also stimulates glutaminase, favoring glutamate uptake and ammonia release from the kidney. Reduced levels of glutamate lead to impaired production of *N*-acetylglutamate (NAGA), a cofactor for carbamoyl phosphate synthetase I (CPS I) which is used in the liver to synthesize urea from ammonia. In humans taking valproic acid, L-carnitine supplementation reduces ammonia concentrations.

VALPROIC ACID AND HEPATOTOXICITY

Valproic acid therapy is associated with a transient dose-related asymptomatic rise in liver enzymes and a rare symptomatic, life-threatening, idiosyncratic, Reyelike, hepatotoxic syndrome. Liver histology of the latter demonstrates microvesicular steatosis, similar to that described in hypoglycin-induced Jamaican vomiting sickness, and Reye syndrome. Numerous studies in patients taking valproic acid demonstrate decreases in both free and total plasma L-carnitine levels, which inhibits the mitochondrial β-oxidation of valproic acid and other fatty acids, causing them to accumulate in the hepatocyte.

Retrospective analysis of patients with acute, symptomatic hepatic dysfunction demonstrates that treatment with L-carnitine significantly improves survival. Early diagnosis, prompt discontinuance of valproic acid, and administration of IV L-carnitine results in the greatest survival.

ADVERSE EFFECTS AND CONTRAINDICATIONS TO L-CARNITINE

L-Carnitine administration is very well tolerated. Transient nausea and vomiting are the most common side effects reported, with diarrhea and a fishy body odor noted at higher doses. The manufacturer of L-carnitine has received case reports of convulsive episodes following L-carnitine use by patients with or without a preexisting seizure disorder. No reports of seizures related to L-carnitine can be found in the human literature. The only data suggesting carnitine-related seizures are found in a rat model.

There are no known contraindications to the use of L-carnitine. However, only the L isomer and not DL-carnitine should be used as the DL mixture may interfere with the mitochondrial utilization of L-carnitine. L-Carnitine is considered category B in pregnancy.

DOSAGE AND ADMINISTRATION

The optimal dosing of L-carnitine for valproic acid-induced hyperammonemia or hepatotoxicity has not been established. Recommendations for intravenous L-carnitine for patients with acute metabolic disorders as a consequence of L-carnitine deficiency range from 50–500 mg/kg/d. A loading dose equal to the daily dose may be initially given, followed by the daily dose divided into every-4-hour doses. We suggest a maximal daily dose of 6 g in addition to the loading dose. The oral dosing of L-carnitine is usually 50–100 mg/kg/d, up to 3 g/d, and should be reserved for patients who are not acutely ill.

For patients with end-stage renal disease on hemodialysis, the package insert recommends an initial intravenous starting dose of 10–20 mg/kg dry body weight over 2–3 minutes after the completion of dialysis followed by an adjustment in the dose according to L-carnitine trough (predialysis) plasma concentrations (normal: 40–50 μmol/L).

For patients with an acute overdose of valproic acid without hepatic enzyme abnormalities or symptomatic hyperammonemia, L-carnitine adminis-

tration can be considered prophylactic and enteral doses of 100 mg/kg/d, divided every 6 hours, up to 3 g/d, is appropriate. For patients with valproic acid-induced symptomatic hepatotoxicity or symptomatic hyperammonemia, intravenous L-carnitine should be administered. We suggest a dose of 100 mg/kg IV up to 6 g administered over 30 minutes as a loading dose, followed thereafter by 15 mg/kg every 4 hours administered over 10–30 minutes.

AVAILABILITY

L-Carnitine is available as a sterile injection for intravenous use (Carnitor) in 1 g/5 mL single-dose vials. L-Carnitine is supplied without a preservative, and once opened, the unused portion should be discarded. Carnitor injection is compatible and stable when mixed with normal saline or lactated Ringer solution in concentrations as high as 8 mg/mL for as long as 24 hours. L-Carnitine as Carnitor is also available as a 330-mg tablet and as an oral solution at a concentration of 100 mg/mL.

48 Antidiabetics and Hypoglycemics

Although various xenobiotics and medical conditions may cause hypoglycemia, the focus of this chapter is on the drugs used in the treatment of diabetes mellitus, which includes insulin and several oral drugs: the sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, and meglitinides. This chemically heterogeneous group of drugs has the potential to cause various unique toxic effects in addition to hypoglycemia.

Hypoglycemia is defined clinically as a serum glucose that produces signs or symptoms of glucose deficit. The glycemic threshold is the plasma glucose concentration below which clinical manifestations develop. This threshold concentration for symptoms to occur is quite variable. In one study, the mean glycemic threshold for hypoglycemic symptoms was 78 mg/dL in poorly controlled diabetics, as compared to 53 mg/dL in nondiabetics.

HISTORY AND EPIDEMIOLOGY

Hypoglycemia is a fairly common occurrence. In various studies approximately 10% of paramedic runs for altered mental status resulted from hypoglycemia; 125 cases of hypoglycemia occurred in one busy emergency department over a year; and hypoglycemia occurred in as many as 20% of patients in a longitudinal study of sulfonylurea use. Attempts to tighten glucose control increase episodes of hypoglycemia. An intensive insulin regimen resulted in 62 episodes of blood glucose <50 mg/dL for every 100 patient years, as compared to only 19 such episodes per 100 patient years using a more conventional regimen. Table 48–1 lists common etiologies for hypoglycemia. In a review of 1418 medication-related cases of hypoglycemia, sulfonylureas alone or with a second agent accounted for 63% of cases.

BIGUANIDE-INDUCED LACTIC ACIDOSIS

The biguanides metformin and phenformin were developed as derivatives of *Galega officinalis,* the French lilac, which was recognized in medieval Europe as a treatment for diabetes mellitus.

Phenformin was used in the United States until 1977, when it was banned because of its association with life-threatening lactic acidosis (64 cases/100,000 patient-years). It is still available in some countries. Metformin became available in the United States in 1995. It is also associated with lactic acidosis, but only about 3 cases/100,000 patient-years.

PHARMACOLOGY

Insulin is synthesized in the β cells of the pancreas as a prohormone, which, upon release, is cleaved, resulting in a C-peptide and in insulin itself. Glucose concentration plays a major role in the regulation of insulin release. Insulin binds to specific receptors on cell surfaces, particularly liver, muscle, and adipose. The action of insulin on these tissues is complex and involves various phosphorylation and dephosphorylation reactions.

The sulfonylureas stimulate the β cells of the pancreas to produce insulin. All the sulfonylureas bind to high-affinity receptors on the pancreatic β-cell

TABLE 48–1. Causes of Hypoglycemia

Endocrine disorders
- Addison disease
- Glucagon deficiency
- Panhypopituitarism (Sheehan syndrome)

Neoplasms
- Carcinomas (diverse extrapancreatic)
- Hematologic
- Insulinoma
- Mesenchymal
- Multiple endocrine adenopathy type 1 (Werner syndrome)

Reactive hypoglycemia

Hepatic disease
- Acute hepatic atrophy
- Alcoholism
- Cirrhosis
- Galactose or fructose intolerance
- Glycogen storage disease
- Neoplasia

Renal disease
- Chronic hemodialysis
- Chronic renal insufficiency

Miscellaneous
- Acquired immunodeficiency syndrome (AIDS)
- Anorexia nervosa
- Autoimmune disorders
- SLE
- Rheumatoid arthritis
- Graves disease
- Burns
- Diarrhea (childhood)
- Leucine sensitivity
- Muscular activity (excessive)
- Postgastric surgery
- Pregnancy
- Protein calorie malnutrition
- Septicemia
- Shock

Exogenous
- Ackee (hypoglycin)
- Alloxan
- β-Adrenergic antagonists
- Disopyramide
- Ethanol
- Antidiabetics (insulin, sulfonylureas)
- Pentamidine
- Propoxyphene
- Quinine
- Quinidine
- Ritodrine
- Salicylates
- Streptozocin
- Sulfonamides
- Vacor
- Valproic acid

Artifactual
- Chronic myelogenous leukemia
- Polycythemia vera

membrane, resulting in closure of potassium channels sensitive to adenosine triphosphate (K_{ATP} channels). This causes membrane depolarization, calcium influx, and activation of the secretory machinery independent of glucose concentration. High-affinity sulfonylurea receptors are also present within pancreatic β cells and are postulated to be either on granular membranes or part of a regulatory exocytosis kinase. Binding to these receptors promotes exocytosis by direct interaction with secretory machinery not involving K_{ATP} channels. Repaglinide and nateglinide are new oral drugs that are structurally different from the sulfonylureas but also bind to K_{ATP} channels.

Metformin lowers glucose by several underlying mechanisms, the most important of which appears to involve the inhibition of gluconeogenesis and subsequent decreased hepatic glucose output. It also enhances peripheral glucose uptake, decreases fatty acid oxidation, and increases intestinal use of glucose. In skeletal muscle and adipose cells, metformin causes enhanced activity and translocation of glucose transporters.

The thiazolidinedione derivatives decrease insulin resistance by the potentiation of insulin sensitivity in the liver, adipose tissue, and skeletal muscle.

Uptake of glucose into adipose tissue and skeletal muscle is enhanced, while hepatic glucose production is reduced.

Acarbose and miglitol are oligosaccharides that inhibit α-glucosidase enzymes in the brush border of the small intestine, mainly glucoamylase, sucrase, and maltase. As a result, postprandial elevations in blood glucose concentrations after carbohydrate ingestion are blunted.

PHARMACOKINETICS AND TOXICOKINETICS

Tables 48–2 and 48–3 outline the major pharmacokinetic parameters of the hypoglycemic agents.

PATHOPHYSIOLOGY

Besides sulfonylurea use, advanced age and fasting are identified as major risk factors for inadvertent hypoglycemia. Intentional overdose of sulfonylureas, repaglinide, and all forms of insulin may produce hypoglycemia through exaggerations of their normal clinical effects. Central nervous system symptoms predominate in hypoglycemia because the brain relies almost entirely on glucose as an energy source. The brain cannot use free fatty acids for fuel because they do not cross the blood–brain barrier. However, during prolonged starvation, the brain is able to use ketones derived from free fatty acids. Other major organs, such as the heart, liver, and skeletal muscle, are able to use various fuel sources, particularly free fatty acids, and are less affected by hypoglycemia.

The autonomic nervous system regulates glucagon and insulin secretion, muscle glycogenolysis, adipose lipolysis, and hepatic glucose production. Propranolol and other nonselective β-adrenergic antagonists affect all these mechanisms and can result in hypoglycemia. In the presence of chronic renal failure, β-adrenergic antagonist-induced hypoglycemia is a particular risk. This likely relates to increased insulin half-life and reduced renal gluconeogenesis. In addition, the clinical presentation of hypoglycemia in diabetics may be muted when β-adrenergic antagonists are used concurrently with hypoglycemics.

The biguanides are unique because of their association with the occurrence of lactic acidosis. Mechanisms for production of lactic acid with phenformin include interference with cellular aerobic metabolism and subsequent enhanced anaerobic metabolism. Phenformin also suppresses hepatic gluconeogenesis from pyruvate and causes a decrease in hepatocellular pH, resulting in decreased lactate consumption and hepatic lactate uptake. Lactic acidosis related to metformin use usually occurs in the presence of an underlying condition, particularly renal impairment.

CLINICAL MANIFESTATIONS

The “classic” findings of hypoglycemia, including tremor, diaphoresis, and tachycardia, are variable in their presentation. Any neuropsychiatric abnormality, whether persistent or transient, focal or generalized, must be considered a possible effect of hypoglycemia, including delirium with subdued, confused, or manic behavior; coma with multifocal brainstem abnormalities; posturing and respiratory abnormalities with preservation of the oculocephalic (doll’s eyes) response, oculovestibular (cold-caloric) response, and pupillary responses; and solitary or multiple seizures, with or without a significant postictal phase. Focal neurologic deficits simulating a cerebrovascular accident (CVA), with or without the presence of coma, occur in approximately 2.4% of cases.

TABLE 48–2. Characteristics of Orally Administered Hypoglycemics*

Drug	Duration of Action (h)	Active Hepatic Metabolite	Active Urinary Excretory Product (% of Dose)	Fecal Excretion (% of Dose)	Frequency of Severe Hypoglycemia (Other Complications)
I. Sulfonylureas					
First generation					
Acetohexamide	12–18	Hydroxyhexamide (+ + +)	Hydroxyhexamide (65%) Acetohexamide (2%)	Negligible	~1%
Chlorpropamide	24–72	2-Hydroxychlorpropamide (+) 3-Hydroxychlorpropamide (+)	Chlorpropamide (20%) 2-Hydroxychlorpropamide (55%) 3-Hydroxychlorpropamide (2%)	Negligible	4–6%
Tolazamide	16–24	Hydroxytolazamide (+ +)	Hydroxytolazamide (35%) Tolazamide (7%)	Negligible	~1%
Tolbutamide	6–12	Hydroxytolbutamide (+)	Hydroxytolbutamide (30%) Tolbutamide (2%)	Negligible	<1%
Second generation					
Glimepiride	24	Cyclohexylhydroxy ethyl derivative (+ +)	Cyclohexylhydroxy methyl derivative (63%)	15%	1–2%
Glipizide	16–24	None	Glipizide (3%)	12%	2–4%
Glyburide	18–24	4-Hydroxyglyburide (+ +)	4-Hydroxyglyburide (36%) Glyburide (3%)	50%	4–6%
II. Biguanides					
Metformin	1.3–4.5	None	Metformin (90%)	Negligible	Rare (lactic acidosis 0.03 cases/1000 patient-years)
Phenformin	6–8	None	Phenformin (66%)	Negligible	Uncommon (lactic acidosis 0.64 cases/1000 patient-years)

(continued)

TABLE 48–2. Characteristics of Orally Administered Hypoglycemics* *(continued)*

Drug	Duration of Action (h)	Active Hepatic Metabolite	Active Urinary Excretory Product (% of Dose)	Fecal Excretion (% of Dose)	Frequency of Severe Hypoglycemia (Other Complications)
III. α-Glucosidase Inhibitors					
Acarbose	2	None	4-Methyl pyrogallol derivative (<2%)	None	None
Miglitol	2	None	100%	None	None
IV. Thiazolidinedione Derivatives					
Pioglitazone	16–24	Hydroxy derivative Keto derivative	?<15–30%	70%	None
Rosiglitazone	12–24	None	None	23%	None
V. Meglitinides					
Nateglinide	2–4	Isoprene derivative (+ +) Hydroxylation metabolites (+)	~16% as parent	10%	<1%
Repaglinide	1–3	None	None	90%	4–6%
VI. Incretin Modulators					
Exentide	12	None	100%	None	Hypoglycemia in overdose
Sitagliptin	24	None	80%	13%	None

+ = Weakly active; + += moderately active; + + += more active than parent drug. The durations of action for the oral drugs are cited for therapeutic doses. These values increase for overdoses.

*Many pharmaceuticals contain combinations of the single agents listed above. The pharmacological and clinical characteristics of each component are relevant with regard to the adverse effects or the overdose setting.

TABLE 48–3. Characteristics of Routinely Used Forms of Insulin

Insulin	Onset of Action (h)	Duration of Action (h)	Peak Glycemic Response (h)
Rapid-acting			
Lispro	0.25-0.5	<5	0.5–2.5
Aspart	0.25	3–5	0.75–1.5
Short-acting			
Regular	0.5–1	5–8	2.5–5
Intermediate-acting			
Lente	1–3	18–24	6–14
NPH	1–2	18–24	6–14
Long-acting			
Ultralente	4–6	20–36	8–20
Basal			
Determir	3–4	5.7–23.2	6–8
Glargine	1.1	24	2–20
Inhaled			
Exubera	0.25	6	2

Sinus tachycardia, atrial fibrillation, and ventricular premature contractions are the most common dysrhythmias associated with hypoglycemia and result from an outpouring of catecholamines, hypoglycemia itself, transient electrolyte abnormalities, and underlying heart disease. Other cardiovascular manifestations include angina, ischemia, and infarction, which may be the sole manifestations of hypoglycemia.

Hypothermia may occur in hypoglycemic patients. If present, hypothermia is usually mild (90–95°F [32–35°C]), unless coexisting conditions are present, such as environmental exposure, infection, head injury, or hypothyroidism.

Hypoglycemia may not occur until 18 hours after lente insulin overdose, and may persist for up to 6 days after ultralente insulin overdose. In a retrospective study of insulin overdose, 7 of 17 cases (41%) developed recurrent hypoglycemia between 5 and 39 hours after overdose, despite oral feeding and intravenous glucose infusion ranging from 5–17 g of glucose per hour. In a retrospective review of 40 sulfonylurea overdose cases, the time from ingestion to the onset of hypoglycemia was variable. The longest delay was 21 hours after ingestion of glyburide, and 48 hours after ingestion of chlorpropamide. In poison center studies of sulfonylurea exposure, the onset of hypoglycemia was from 0.5–21 hours after ingestion. Single-tablet ingestions of sulfonylureas can result in delayed hypoglycemia in young children.

Case reports document the occurrence of severe lactic acidosis after metformin overdose. Although rare, hypoglycemia has also been reported. Many patients on metformin also take sulfonylureas, so hypoglycemia should be anticipated after overdose.

Repaglinide, nateglinide, troglitazone, rosiglitazone, pioglitazone, and acarbose are newer drugs for which overdose data are limited. Hypoglycemia should be anticipated after repaglinide and nateglinide ingestion. Although hypoglycemia would not be expected after thiazolidinedione overdose, experience is limited. There are case reports of hepatic toxicity related to the ther-

apeutic use of rosiglitazone and pioglitazone. It is unlikely that acarbose would cause hypoglycemia. The most common adverse effects associated with therapeutic use are gastrointestinal, including nausea, bloating, abdominal pain, flatulence, and diarrhea. Hepatotoxicity related to therapeutic use of acarbose is reported, but appears to resolve after discontinuation of the drug.

DIAGNOSTIC TESTING

Serum glucose concentrations are accurate, but treatment cannot be delayed pending the results. Glucose reagent strip testing can be performed at the bedside, and sensitivity for detecting hypoglycemia is excellent, but these tests are imperfect. It is important to remember that hypoglycemia is a clinical disorder, not a numerical disorder. Patients with poorly controlled diabetes, in particular, may become symptomatic at higher glucose concentrations than those without the disease. The threshold reagent strip concentrations that should be used for the administration of hypertonic dextrose may be debated, but we would argue that based on the available data, a cutoff of <90 mg/dL is appropriate in symptomatic patients.

Other than glucose determinations, various diagnostic studies may be indicated, depending on the clinical situation. Renal function tests may indicate the presence of renal impairment as a causative factor of hypoglycemia. Hepatic function tests may be a clue to liver disease as a cause of hypoglycemia, although this may also be evident on physical examination. Numerous other medical conditions, as well as various drugs, may be involved (Table 48–1), and diagnostic testing will be tailored to each individual episode depending on the clinical suspicion.

EVALUATION OF MALICIOUS, SURREPTITIOUS, OR UNINTENTIONAL INSULIN OVERDOSE

When the plasma glucose is less than 45 mg/dL, insulin secretion should be almost completely suppressed and plasma insulin concentrations should be minimal or absent. Moreover, insulin is secreted as proinsulin, which is cleaved in vivo to form insulin (a double-stranded peptide) and C-peptide, which are released into the blood in equimolar quantities. Although insulin is normally cleared during hepatic transit, C-peptide is not; consequently, C-peptide can be used as a quantitative marker of endogenous insulin secretion. Commercially available exogenous human insulin does not contain C-peptide fragments (Table 48–4).

MANAGEMENT

Treatment centers on the correction of hypoglycemia and the anticipation that hypoglycemia may recur in the overdose setting. Symptomatic patients with hypoglycemia require immediate treatment with 0.5–1 g/kg of concentrated intravenous dextrose in the form of $D_{50}W$ (50% dextrose in water) in adults, $D_{25}W$ (25% dextrose in water) in children, and $D_{10}W$ (10% dextrose in water) in neonates. Occasionally, patients require a larger dose to achieve an initial response. Although the use of concentrated dextrose has some theoretical risks, such as in the setting of cerebral ischemia, failure to rapidly correct hypoglycemia may lead to deleterious neurologic effects. An intravenous dose of 100 mg of thiamine hydrochloride should be given as well in view of the substantial association of hypoglycemia with alcoholism and malnutrition. Glucagon should not be considered except in the uncommon situation in which intravenous access cannot be obtained. Glucagon requires time to take effect and may be ineffective in patients with depleted glycogen stores.

TABLE 48–4. Laboratory Assessment of Fasting Hypoglycemia

Clinical State	Insulin[a] (Plasma) (μUnit/mL)	C-Peptide (Plasma) (nmol/L)	Proinsulin (pmol/L)	Antiinsulin Antibodies[c]
Normal	<6	<0.2	<5	—
Exogenous insulin	Very high	Low (suppressed)	Absent	Present[d]
Insulinoma	High	High	Present	Absent
Sulfonylurea ingestion[b]	High	High	Present	Absent
Autoimmune	Very high (artifact)	Low (or) high (artifact)	Present	Present
Decreased glucose production	Low	Low	Present	Absent
Neoplasia (non–β-cell)	Low	Low	Present	Absent

[a]Insulin concentrations are determined during fasting hypoglycemia at low concentrations, preferably <60 mg/dL of blood glucose.
[b]Sulfonylurea ingestion is diagnosed by detection of the drugs or their metabolites in plasma or urine.
[c]The antiinsulin antibodies produced spontaneously differ from those of treated (exposed to exogenous insulin) and those of untreated insulin-dependent diabetics.
[d]The presence of antiinsulin antibodies occurs less frequently in those exposed only to human insulin.

The benefits of emesis, lavage, and catharsis should be considered in managing a patient with an overdose of oral hypoglycemic drugs. The extensive affinity between chlorpropamide, tolazamide, tolbutamide, glyburide, glipizide, and carbutamide and activated charcoal has been demonstrated in vitro. Single-dose activated charcoal, and possibly multiple-dose activated charcoal, theoretically should be beneficial in the management of these overdoses. Urinary alkalinization to a pH of 7–8 can reduce the half-life of chlorpropamide from 49 hours to approximately 13 hours. Urinary alkalinization is not useful for other oral drugs.

MAINTAINING EUGLYCEMIA AFTER INITIAL CONTROL

After the patient is awake and alert, further therapy depends on the drug involved and pancreatic islet cell function. One problem that occurs with dextrose administration is that individuals who can produce insulin through glucose-stimulated insulin release (nondiabetics and those with type II diabetes mellitus) are at substantial risk of recurrent hypoglycemia. Thus treatment with hypertonic dextrose solutions can be expected to result in dramatic, yet transient, increases in glucose concentrations, with a subsequent fall in serum glucose possibly to hypoglycemic concentrations again.

Following insulin overdose, feeding should be initiated and glucose concentrations maintained in the 100–150 mg/dL range with intravenous dextrose. Concentrated dextrose infusion may be required. Central venous lines should be used when an infusion of 20% dextrose is instituted, as the solution is a substantial venous irritant. The appropriate timing of glucose monitoring

varies depending on the clinical situation. Mental status must be observed as well. As a rough guide, glucose monitoring every 1–2 hours after initial control is reasonable, with subsequent spacing of the intervals to once every 4–6 hours. Potassium and phosphate concentrations must also be monitored, as glucose administration may lead to hypokalemia and hypophosphatemia.

After initial control of hypoglycemia has been obtained following overdose of sulfonylureas or meglitinides the patient should be fed. Intravenous access is necessary, but routine dextrose infusion should be avoided. As with insulin overdose, frequent monitoring of glucose concentrations and mental status is critical. We recommend early use of octreotide in this setting because of the significant risk of glucose-stimulated insulin release (see Antidotes in Brief: Octreotide). The suggested octreotide dose is 50 μg subcutaneously every 6 hours in adults and 1–1.5 μg/kg every 6 hours up to the adult dose in children.

ADMITTING PATIENTS TO THE HOSPITAL

The decision to admit a patient is difficult, but several guidelines may be followed. Admission is required for hypoglycemia related to ethanol, starvation, hepatic failure, and renal failure, as well as in hypoglycemia of unknown etiology. Patients on therapeutic doses of insulin require inpatient evaluation of recurrent and unexplained hypoglycemic episodes. All patients who present with hypoglycemia caused by a sulfonylurea or after unintentional overdose with long-acting insulin should be admitted. Hospitalization is recommended after unintentional overdose with ultrashort-, short-, or intermediate-acting insulin if hypoglycemia is persistent or recurs during a 4–6 hour observation period in the emergency department. Admission is also indicated for any patient, regardless of serum glucose or symptoms, who intentionally overdoses on a sulfonylurea or any form of insulin, as delayed, profound, and protracted hypoglycemia may result. Children who have unintentionally ingested as little as 1 sulfonylurea tablet should be admitted. Although this is controversial and some authors have suggested shorter observation periods, and even home monitoring in some cases, we feel that the delayed effects of sulfonylurea ingestion in children are well documented in the literature and convincing enough to support our position.

In patients with metformin-associated lactic acidosis, it is essential to maintain a near-normal pH and to exclude other potential causes of lactic acidosis, such as ischemia and infection. Hypertonic sodium bicarbonate may be used, but patients often become volume overloaded secondary to concomitant renal insufficiency. Hemodialysis or other renal replacement therapies may be required to control salt and water balance and pH when patients cannot tolerate hypertonic sodium bicarbonate. Although a typical course of hemodialysis only removes a few therapeutic doses of metformin, this, along with control of the acid–base and fluid and electrolyte abnormalities, appears sufficient to improve outcome.

Dextrose

Adenosine triphosphate (ATP) furnishes the metabolic energy that fuels critical cellular processes in all organs. In the adult human brain, the anaerobic and aerobic metabolism of glucose through glycolysis and the tricarboxylic acid cycle, respectively, are the primary sources of ATP. The onset of hypoglycemia is followed rapidly by cerebral dysfunction. Hypoglycemia causes neurologic effects that are clinically indistinguishable from those of a variety of toxic-metabolic and structural brain injuries that can include focal stroke syndromes, seizures, confusion, delirium, and coma. Hypoglycemia also precipitates myocardial stress and is associated with angina, electrocardiographic changes, and dysrhythmias. Although in most cases these effects reverse following treatment of hypoglycemia, prolonged or severe hypoglycemia may result in permanent brain injury, myocardial infarction, and death.

THE CLINICAL MANIFESTATIONS ASSOCIATED WITH HYPOGLYCEMIA

Symptoms of tachycardia, diaphoresis, pallor, hypertension, tremors, hunger, anxiety, and restlessness tend to predominate when the decline in blood glucose is rapid. Central nervous system symptoms of glycopenia include headaches, visual disturbances, psychiatric disturbances, confusion, stupor, coma, seizures, and focal neurologic findings and are nonspecific. In children, the only symptom of neuroglycopenia may be lethargy or irritability. Unfortunately, neither the history nor the physical examination reliably detects patients who are hypoglycemic.

THE RELIABILITY OF BEDSIDE BLOOD GLUCOSE DETERMINATIONS

The bedside diagnosis of hypoglycemia is also limited by the lack of availability of reagent strips that have the same reliability and accuracy of the chemistry laboratory. Sensitivities of commonly available reagent strips for the detection of hypoglycemia range between 92% and 97% in various studies. The accuracy of these tests is affected by the source of blood, whether venous or capillary; and by the presence of shock. In addition, it may also be altered by the hematocrit, or the presence of isopropyl alcohol in the sample. False-positive capillary determinations of hypoglycemia have been demonstrated in patients with shock and cardiac arrest. Also, the agreement between reagent strip determinations of capillary and venous blood is poor in the normoglycemic range, with a tendency for capillary measurements to correlate more closely with the laboratory and to be higher than venous measurements. Finally, although false-negative tests are uncommon, elevated acetaminophen concentrations tend to produce false elevations of reagent strips tests of glucose.

In addition, poorly controlled diabetics experience hypoglycemic symptoms at blood glucose concentrations that would normally be regarded as euglycemic. In one study where hypoglycemia was defined as a blood glucose concentration <60 mg/dL, 2 of 33 hypoglycemic patients were missed. A cutoff of 90 mg/dL would have detected 100% of clinically hypoglycemic patients.

PHARMACOKINETICS OF DEXTROSE

Studies of the pharmacokinetics of dextrose are limited, making it difficult to predict the amount of dextrose required to effectively treat hypoglycemia. It can be calculated that, at equilibrium, 25 g of dextrose distributed in total body water in a 70-kg adult would raise the serum glucose by about 60 mg/dL. In the few clinical studies that have been done, the magnitude of the glucose elevation after oral or intravenous loading is highly unpredictable. In one study, the intravenous administration of 25 g (50 mL) of $D_{50}W$ (50% dextrose in water) to adults resulted in a mean blood glucose elevation of 166 mg/dL; however, the range was 37–370 mg/dL above baseline. In a human model of insulin-induced hypoglycemia, the oral administration of 20 g of dextrose raised serum blood glucose concentration from 60 mg/dL to 120 mg/dL over 1 hour, whereas 10 g raised the concentration from 60 mg/dL to 100 mg/dL.

CONTROVERSY REGARDING ELEVATED BLOOD GLUCOSE CONCENTRATIONS IN THE PATIENT WITH CEREBRAL ISCHEMIA

Controlled laboratory investigations of ischemic brain injury consistently demonstrate that higher blood glucose concentrations are associated with more extensive cerebral injury. Similarly, an expanding body of clinical literature demonstrates that admission hyperglycemia is associated with poorer outcomes in patients with acute cerebrovascular accidents. Controversy exists over the inability to delineate the primary effect of hyperglycemia on the ischemic brain from hyperglycemia that accompanies an intense sympathetic "stress" response to severe brain injury.

None of these studies, however, adequately addresses the effects of a single dose of dextrose given after injury. Despite that fact, these clinical and laboratory studies have led to calls for reassessment of the standard practice of routine administration of hypertonic dextrose in patients with altered mental status. There is no question that the reversal of hypoglycemia is a sound clinical intervention in the patient who is hypoglycemic, and that the failure to administer dextrose in a timely fashion to a patient with significant hypoglycemia can result in permanent neurologic injury.

Patients with focal neurologic deficits caused by ischemia constitute a population that would reasonably be expected to have the greatest benefit from the maintenance of euglycemia. Although focal presentations of hypoglycemia are not rare, they are infrequent relative to the numbers of patients with focal presentations who have suffered cerebrovascular accidents. In one study, nearly 3% of patients with hypoglycemia presented with focal symptoms. In the patient with a history of diabetes who presents with focal symptoms, symptomatic hypoglycemia must be strongly considered when the reagent strip shows a blood glucose level of less than 90 mg/dL.

DOSING AND ADMINISTRATION

Patients with altered mental status should receive hypertonic dextrose if the bedside glucose test is less than 90 mg/dL. When a reliable bedside glucose determination is not readily available, all patients with altered mental status should receive hypertonic dextrose empirically.

The administration of 0.5–1 g/kg of concentrated intravenous dextrose immediately reverses the clinical effects of uncomplicated hypoglycemia when

TABLE A–11–1. Dosing of Dextrose

Bolus	
Adult	
$D_{50}W$ (50% = 0.5 g/mL)	0.5–1.0-g/kg bolus
Child	
$D_{25}W$ (25% = 0.25 g/mL); 1:1 dilution of $D_{50}W$ with sterile water	0.5-g/kg bolus
Infant	
$D_{10}W$ (10% = 0.1 g/mL); 1:4 dilution of $D_{50}W$ with sterile water	0.5-g/kg bolus
Infusion	
Adults and children	
$D_{10}W$ (10% = 0.1 g/mL) D_5W (5% = 0.05 g/mL)	Titrate infusion as indicated to maintain serum glucose in normal range

the duration of hypoglycemia has been brief (Table A–11–1). Clinically insignificant or very rare complications of this practice include hypophosphatemia, hyperkalemia in diabetic patients with type IV renal tubular acidosis, pulmonary edema secondary to osmotic effects, lactic acidosis in cancer patients with large tumor burdens, and phlebitis and sclerosis of veins. Inappropriately large boluses of $D_{50}W$ in children are also associated with seizures, hyperosmolar coma, and death.

Octreotide

HISTORY

"Somatostatin" is a collective term for several shorter fragments cleaved from preprosomatostatin and prosomatostatin. In addition to its effects on growth hormone and insulin secretion, somatostatin, has far-reaching effects as a central nervous system (CNS) neurotransmitter and as a modulator of hormonal release. Unfortunately, the role for somatostatin is limited because it is short acting. Octreotide was synthesized as a longer-acting analog of somatostatin.

PHARMACOLOGY

Somatostatin's effects are mediated by high-affinity binding to 5 different membrane receptors, numbered SSTR 1–5, on target tissues. Octreotide has high binding affinity for SSTR 2 and 5 subtypes, low binding affinity for SSTR 1 and 4 subtypes, and intermediate binding affinity for SSTR 3 subtype. SSTR 2 is found in the pancreas, brain, pituitary, stomach, and kidney, whereas SSTR 5 is found in the brain, pituitary, heart, adrenal glands, placenta, small intestine, and skeletal muscle.

Somatostatin inhibits insulin secretion by a G-protein–mediated decrease in calcium entry through voltage-dependent Ca^{2+} channels. Experiments with somatostatin, both in healthy human volunteers and in an isolated perfused canine pancreas model, demonstrate that somatostatin inhibits glucose-stimulated insulin release. Additionally, somatostatin inhibits the insulin response to glucagon. These effects of somatostatin are short-lived.

PHARMACOKINETICS

Following IV administration, the distribution half-life of octreotide in human volunteers averages 12 minutes and the elimination half-life ranges from 72–98 minutes. The volume of distribution is 18–30 L. Renal elimination accounts for approximately 30% of the elimination and is reduced in the elderly and in those with severe renal failure.

After subcutaneous administration, bioavailability is 100% and peak levels are achieved within 30 minutes. The elimination half-life was 88–102 minutes. Peak plasma concentrations are approximately half of the intravenously administered concentration.

CLINICAL USE FOR INSULIN SUPPRESSION

Octreotide was studied in several clinical conditions, including insulinomas and hypoglycemia of infancy. In most instances, octreotide suppressed insulin concentrations, and glucose concentrations rose. However, hypoglycemia may worsen when glucagon suppression outlasts insulin suppression. Octreotide is currently used for the treatment of drug-induced endogenous secretion of insulin.

Several case studies and a case series of 9 patients support the efficacy of octreotide in overdoses of glipizide, glyburide, gliclazide, and tolbutamide.

The most common doses used were on the order of 50–100 μg subcutaneously repeated every 8–12 hours in the adult patients.

ADVERSE EFFECTS

Octreotide is generally well tolerated but experience in the toxicologic setting is limited. Adverse reactions occurring with short-term administration are usually local or gastrointestinal in nature. Stinging at the site of injection occurs in approximately 7% of patients, but rarely lasts more than 15 minutes. In volunteers, no significant side effects occur with intravenous doses of 25 or 50 μg, or with subcutaneous doses of 50 or 100 μg. At higher doses, early transient nausea and later-appearing, but longer-lasting, diarrhea and abdominal pain frequently occur. Healthy volunteers were given IV bolus doses as high as 1000 μg and infusion doses of 30,000 μg over 20 minutes and 120,000 μg over 8 hours without serious adverse effects.

DOSING ADMINISTRATION

Both subcutaneous and intravenous administration are acceptable, although the usual route of administration is subcutaneous. Using the smallest volume possible reduces the pain with subcutaneous administration. There are no controlled trials evaluating the dose of octreotide in the management of sulfonylurea overdose. A 50-μg subcutaneous dose of octreotide every 6 hours is suggested to treat adults. In children, a dose of 4–5 μg/kg/d subcutaneously divided every 6 hours, up to the adult dose, may be used for initial therapy. Several days of therapy might be required, depending on the duration of the offending xenobiotic. All patients must be carefully monitored for recurrent hypoglycemia during octreotide therapy, and for perhaps 24 hours following termination of octreotide therapy prior to discharge.

AVAILABILITY

Octreotide acetate (Sandostatin) injection is available in ampules and multidose vials ranging in concentration from 50–1000 μg/mL. The multidose vials contain phenol.

49 Thyroid and Antithyroid Medications

HISTORY AND EPIDEMIOLOGY

In 1891, the injection of ground sheep thyroid extract was formally described as a treatment for myxedema. Seaweed, which contains large amounts of iodine, was used to treat goiter (hypothyroidism) in Chinese medicine as early as the 3rd century A.D. In 1863, Trousseau fortuitously discovered a treatment for Graves disease when he inadvertently prescribed daily tincture of iodine instead of tincture of digitalis to a tachycardic, thyrotoxic young woman.

Triiodothyronine (T_3) was not isolated and synthesized until the 1950s. Prior to this, desiccated animal thyroid gland was commonly used to treat hypothyroidism. Two epidemics of *hamburger thyrotoxicosis* occurred in the United States in the mid 1980s, secondary to consumption of ground beef contaminated with bovine thyroid gland.

Hypothyroidism affects 1–7% American adults, and in 2003, thyroxine (Synthroid; T_4) was the second most frequently prescribed medicine. There are many reports of intentional and unintentional overdoses with thyroid hormone. Despite the profound effects of thyroid hormones on physiologic homeostasis and the widespread use and access to exogenous thyroid hormone, morbidity and mortality from overdose overall are very low.

PHYSIOLOGY

Thyroid function is influenced by the hypothalamus, the pituitary gland, the thyroid gland, and the target organs for the thyroid hormones. The hypothalamus produces thyroid-releasing hormone (TRH), which is transported through the venous sinusoids to the pituitary gland, which releases thyroid-stimulating hormone (TSH). TSH enters the circulation and stimulates the production and release of thyroid hormones (T_3 and T_4) by the thyroid gland. Thyroid hormones exhibit feedback control of hormonal function, by having an inhibitory effect on the pituitary gland.

Roughly 95% of circulating or *peripheral* thyroid hormone is T_4, and the remainder is T_3. Only 15% of the peripheral T_3 is secreted directly by the thyroid; the balance is a result of the peripheral conversion of T_4 to T_3. T_3 has approximately 3 times greater hormonal activity than T_4.

PHARMACOLOGY

Table 49–1 outlines some important pharmacokinetic properties of thyroid hormones. Gastrointestinal absorption can be decreased by variations in intestinal flora and binding by agents such as aluminum-containing antacids, calcium preparations, carbonate salts, sucralfate, iron, bile acid sequestrants (ie, cholestyramine resins, colestipol hydrochloride), and infant soy formula. Thyroid hormones undergo their ultimate metabolism peripherally. Intracellular sequential deiodination accounts for approximately two-thirds of inactivation. Most of the remaining one-third undergoes hepatic metabolism by glucuronidation or sulfation. Xenobiotics that induce hepatic microsomal metabolism, such as rifampin, phenobarbital, phenytoin, and carbamazepine, increase the metabolic clearance of T_3 and T_4.

TABLE 49–1. Pharmacokinetic Properties of Thyroid Hormones

Pharmacokinetic Property	T_3	T_4
Oral bioavailability (exogenous drug)	95%	80%
Volume of distribution (L/kg)	40	10
Half-life (days)	1	7
Protein binding (normal adult)	99.96%	99.6%
Relative potency	4	1

PATHOPHYSIOLOGY

Thyroid hormones are critical for optimal physiologic growth and function. Thyroid function is the most important determinant of basal metabolic rate (BMR). Additionally, the thyroid exercises a permissive effect on many hormones, notably catecholamines and insulin.

When an excess of active thyroid hormone exists, the condition is known as hyperthyroidism. Most aspects of carbohydrate and protein metabolism are increased in the presence of thyroid hormone excess. Lipid metabolism is also increased and there is an increase in cholesterol synthesis. The clinical picture consists of the manifestations of increased metabolism, along with tachycardia, tremor, anxiety, and other behavioral changes, and sometimes tachydysrhythmias such as atrial fibrillation. An increased sensitivity to catecholamines underscores the sympathomimetic effects on inotropy and chronotropy produced by thyroid hormones. T_3 increases the number of β-adrenergic receptors in various tissues, including cardiac cells. T_3 also modulates myocyte intracellular signaling mechanisms that lead to increased catecholamine effects.

CLINICAL MANIFESTATION

The widespread availability and use of thyroid supplements make it a common etiology of acute intentional and unintentional overdoses. In addition, chronic excess thyroid hormone ingestion is a relatively frequent occurrence. Symptoms of toxicity from exogenous thyroid hormone resemble those of catecholamine excess, such as tachycardia, tachydysrhythmias (usually atrial fibrillation or flutter), thromboembolism, and cardiac failure. Hyperthermia occurs either secondary to the thermogenic effects of thyroid hormones or from psychomotor agitation.

Acute Toxicity

Acute overdoses with thyroid hormone preparations most commonly occur with oral levothyroxine. Significant ingestions of levothyroxine usually do not manifest clinically until 7–10 days after the exposure, but are (rarely) reported to manifest as early as 2–3 days after ingestion. Slow peripheral conversion of T_4 to T_3 and the time to nuclear receptor activation and protein synthesis account for this latency. In contrast, acute overdoses involving preparations containing T_3 can manifest in the first 12–24 hours days after exposure.

In children, acute thyroxine overdoses are almost universally benign owing to their typically unintentional nature and lower doses ingested. Most remain asymptomatic or only develop mild symptoms. Ingestions in adults have a wide range of toxicity. Symptoms can resemble thyrotoxicosis, and in extreme cases, thyroid storm. Hyperthermia, dysrhythmias, and severe agitation are well described. Hemiparesis, muscle weakness, coma, respiratory failure, sudden death, myocardial infarction, cardiac failure, focal myocarditis, rhab-

domyolysis with muscle necrosis, delayed palmar desquamation (more than 2 weeks after ingestion), and hematuria are also described.

Chronic Toxicity

Following chronic excessive thyroid hormone ingestions, patients may present with thyrotoxicosis or a have a more subtle and insidious presentation. Classically, the chronic ingestion of excess thyroid hormone occurs in patients with hypothyroidism, psychiatric disorders, and eating disorders. Significant weight loss, anxiety, and accelerated osteoporosis can develop. More severe manifestations, as described above, can also occur.

DIAGNOSTIC TESTING

Traditionally, thyroid testing was undertaken using combinations of measurements of total T_4, and some measurement of hormone binding (T_3 uptake). Assessment of the pituitary production of TSH has greatly improved in recent years. Supersensitive (third-generation) assays for TSH are now the primary tests used for screening. Suppressed or elevated concentrations of TSH can be reflexively followed up with a free T_4 assay and, if necessary, a total T_3 assay (Table 49–2).

The clinical manifestations of thyrotoxicosis and thyroid storm are well known to occur at normal, low, moderate, and high concentrations of T_3 and T_4. This lack of correlation between symptoms and serum concentrations is also true for exogenous thyroid hormone ingestion. Routine analysis of laboratory thyroid function tests in the setting of acute thyroid hormone overdose is unlikely to affect management.

MANAGEMENT

General

Based on the existing literature, conservative management is adequate in most cases of acute, unintentional thyroxine ingestions in both adults and children. Most children with acute overdose are managed with home observation and followup appointments. Gastrointestinal decontamination is rarely

TABLE 49–2. Diagnostic Tests for Thyroid Hormone and Thyroid Function

Diagnostic Test	Normal Values[a]	Comments
TSH	0.5–5.0 μIU/mL	Available assays with respective detection limits: First generation = 1.0 μIU/L Second generation = 0.1 μIU/L Third generation = 0.01 μIU/L
Total T_4 by RIA	5–12 μg/dL (64–153 nmol/L)	↑ In pregnancy, estrogens, oral contraceptives
Total T_3 by RIA	40–132 ng/dL (1.1–2.0 nmol/L)	↑ In pregnancy, estrogens, oral contraceptives
Free T_4	0.7–1.86 ng/dL (9–24 nmol/L)	↑ In hyperthyroidism, exogenous thyroxine ingestion
Free T_3	0.2–0.52 ng/dL (3–8 nmol/L)	↑ In hyperthyroidism, exogenous thyroid hormone (T_3 or T_4)

RIA, radioimmunoassay; TSH, thyroid-stimulating hormone.
[a]Interlaboratory and interassay variations may occur.

necessary. Activated charcoal administration should be considered in both adults and children if the ingestion is greater than 5000 μg of thyroxine and no contraindications exist. Except in early presentations with massive intentional thyroxine ingestions (>10,000–50,000 μg) in suicidal adults or ingestions of preparations containing large amounts of T_3, gastric-emptying procedures, such as induced emesis and orogastric lavage, are unwarranted.

Treatment should be based on the development of symptoms and should include rehydration, airway protection, and control of sympathomimetic symptoms, mental status alterations, and hyperthermia. β-Adrenergic antagonism with propranolol has been used for sympathomimetic symptoms in numerous cases. Empiric treatment with β-adrenergic antagonists is not recommended. β-Adrenergic antagonists should be given for significant tachycardia, dysrhythmias, and other symptoms of catecholamine excess. When sedation is required, parenteral benzodiazepines and barbiturates are recommended. Sedation with antipsychotics such as haloperidol and droperidol should be avoided because their significant anticholinergic properties can exacerbate thyrotoxic symptoms. In addition, these drugs may prolong the QTc and predispose to malignant dysrhythmias.

The principal mechanism of action of β-adrenergic antagonists in hyperthyroidism is antagonism of β-receptor-mediated effects. In addition to their sympatholytic effects, β-adrenergic antagonists inhibit 5-deiodenase, thereby decreasing peripheral conversion of T_4 to T_3. Propranolol is the most frequently used β-adrenergic antagonist in thyrotoxic patients. Starting doses of 1–2 mg of propranolol IV every 10–15 minutes are recommended. Very high doses may be required. Oral propranolol can be used for symptoms in patients who are both hemodynamically and medically stable. Oral doses, in the range of 20–120 mg every 6 hours, may be required. When β-adrenergic antagonists are contraindicated, such as in patients with asthma or severe congestive heart failure, calcium channel blockers may be used.

Antipyretics are recommended for hyperthermia, and acetaminophen is the drug of choice. Aspirin, particularly high doses (1.5–3 g/d), should be avoided as it carries a theoretical risk of increased thyrotoxicity from displacement T_3 and T_4 from thyroxine-binding globulin. It is important to note, however, that hyperthermia, especially extreme hyperthermia (>106°F [41°C]), is most likely secondary to psychomotor agitation and excess heat production from the hypermetabolic, catecholaminergic, thyrotoxic state. Extreme hyperthermia should be rapidly and aggressively treated with active external cooling with ice baths as well as β-adrenergic antagonism, sedation with benzodiazepines and/or barbiturates, and intubation with paralysis if necessary.

Other therapies typically used for hyperthyroidism have little, if any, role in either acute or chronic overdose. However, there may be a role for early plasmapheresis in the exceptional situation of a known massive ingestion of thyroid hormone. Because the outcomes from most ingestions of thyroid hormone will be favorable with good supportive care, sedation, and β-adrenergic antagonism, the risks of plasmapheresis should be evaluated on a case-by-case basis after consultation with a medical toxicologist.

XENOBIOTICS WITH ANTITHYROID EFFECTS

Thioamides

Methimazole and propylthiouracil (PTU) are the two principal thioamides used in the treatment of hyperthyroidism. Carbimazole, which is bioactivated methimazole, is available in Europe and China. Methimazole and PTU both

TABLE 49–3. Common Xenobiotics That Alter Thyroid Function and Cause Clinically Important Effects

Xenobiotic	Effect	Mechanism
Lithium	Goiter (in 37% of patients) Hypothyroidism (in 5–15% of patients)	Mechanism unclear
Amiodarone (37% iodine by weight)	1. Hypothyroidism (in 25% of patients) ↓ Peripheral conversion of T_4 to T_3	1. Inhibition of 5-deiodinase
	2. Hyperthyroidism, type 1: in patients with preexisting goiters from low iodine intake	2. Type 1: iodine excess stimulates thyroid hormone production
	3. Hyperthyroidism, type 2: in patients with previously normal thyroid function	3. Type 2: causes thyroid inflammation
β-Adrenergic antagonists	↓ Peripheral conversion of T_4 to T_3	Inhibition of 5'-deiodinase
PTU	Decreased thyroid hormone synthesis	Inhibition of thyroid peroxidase
	↓ Peripheral conversion of T_4 to T_3	Inhibition of 5'-deiodinase
Corticosteroids	↓ Peripheral conversion of T_4 to T_3	Inhibition of 5'-deiodinase
Iodine	1. Low dose: transient or no effect	1. Transiently stimulates thyroid hormone secretion
	2. High doses (>10 g/d): thyroid hormone secretion	2. Inhibition of thyroid hormone synthesis
	3. Transient thyrotoxicosis (ie, Jod-Basedow effect)	3. Increases thyroid hormone synthesis
	A. With rapid correction of hypothyroidism from iodine deficiency	4. Mechanism unclear
	B. From topical iodine	5. Direct cytotoxic injury to cells
	4. Delirium	
	5. Caustic injury	
Iodinated contrast material	1. Rapid ↓ peripheral conversion of T_4 to T_3 (adjunctive treatment in thyroid storm)	1. Inhibition of 5-deiodinase
	2. Prolonged suppression of T_4 to T_3	2. Mechanism unclear
	3. Causes thyrotoxicosis and thyroid storm	3. Mechanism unclear
	4. Iodide mumps	4. Idiopathic, toxic accumulation of iodide
Radioactive iodine	Treatment of hyperthyroidism, causes hypothyroidism	Uptake into thyroid follicles causes local destruction
Anion inhibitors[a]	↓ Iodine uptake into thyroid follicle, used in iodide-induced hyperthyroidism	Blocks uptake of iodide into the thyroid gland by competitive inhibition

[a]Also referred to as monovalent anions, ie, thiocyanate (SCN^-), pertechnetate (TcO_4^-), and perchlorate (ClO_4^-).

inhibit the activity of *thyroid peroxidase* in the thyroid gland. PTU has the added effect of inactivation of 5-deiodinase, which decreases the peripheral conversion of T_4 to the metabolically more active T_3.

Adverse effects occur in 3–12% of patients taking thioamides. The most common adverse effect is a maculopapular pruritic rash. Methimazole, PTU, and to a lesser extent carbimazole, can cause immune-mediated, dose-, and age-related agranulocytosis and neutrophil dyscrasias and LFT abnormalities. This potentially life-threatening adverse effect can be treated by administration of granulocyte colony-stimulating factor. Premature withdrawal of thioamides can lead to rebound symptoms and thyrotoxic states.

Very little data exist regarding overdose with thioamides. A 12-year-old girl with a previous thyroidectomy, who was estimated to have ingested 5000–13,000 mg of PTU, developed only a transient decreased T_3 and elevated alkaline phosphatase. No other serious sequelae have been associated with acute overdose of thioamides.

Iodides

Prior to the development of thioamides, iodide salts were the principal treatment for hyperthyroidism. Iodides decrease thyroid hormone concentrations by inhibiting formation and release. In thyroid storm, high-dose iodides (>2 g/d) decrease thyroid hormone release and produce substantial improvements by 2–7 days.

The adverse reaction to excessive amounts of iodide salts, termed *iodism*, is characterized by cutaneous rash, laryngitis, bronchitis, esophagitis, conjunctivitis, drug fever, metallic taste, salivation, headache, and bleeding diathesis. Immune-mediated hypersensitivity symptoms consisting of urticaria, angioedema, eosinophilia, vasculitis, arthralgia, or lymphadenitis, and, rarely, anaphylactoid reactions can occur. Chronic iodide therapy has also produced goiters, hypothyroidism, and, rarely, hyperthyroidism. Iodide mumps is a well-described, but rare disorder that is characterized by severe sialadenitis (or parotitis), allergic vasculitis, and/or conjunctivitis following administration of ionic and nonionic iodine-containing contrast media and oral iodide salts. Symptoms tend to occur within 12 hours and resolve spontaneously within 48–72 hours. As much as 10 g of sodium iodide has been administered IV without development of signs or symptoms of toxicity.

Table 49–3 summarizes xenobiotics that alter thyroid effects.

50 Antihistamines and Decongestants

ANTIHISTAMINES

History and Epidemiology

Antihistamines (H_1 receptor antagonists) were introduced into clinical use in the early 1940s and the class continues to find widespread application in the treatment of anaphylaxis, allergic rhinitis, urticaria, and other histamine-mediated disorders. Antihistamines are available worldwide, many without a prescription. Unintentional exposures to antihistamine-containing preparations are also very common with more than 14,000 cases involving children younger than 6 years of age reported annually to US poison centers. Cases of intentional abuse and suicide are also common.

Physiology of the Histamine Receptor System

Four types of histamine receptors are recognized (H_1, H_2, H_3, and H_4), all of which are coupled to G proteins. H_1 receptors are located in the CNS, heart and vasculature, airways, sensory nerves, gastrointestinal smooth muscle cells, immune cells, and the adrenal medulla, and control the sleep–wake cycle, cognition, memory, and endocrine homeostasis, among others. Stimulation of the H_1 receptor also causes vasodilation, increases vascular permeability, bronchoconstriction, and decreases atrioventricular nodal conduction. H_2 receptors are located in cells of the gastric mucosa, heart, lungs, CNS, uterus, and immune cells where stimulation increases gastric acid secretion and vascular permeability. H_3 receptors are found in neurons of the central and peripheral nervous system, airways, and the GI tract, where they provide feedback inhibition of histamine, acetylcholine, dopamine, norepinephrine, and serotonin release. The recently identified H_4 receptor is located in leukocytes, bone marrow, the spleen, lungs, liver, colon, and hippocampus, and apparently has roles in the differentiation of myeloblasts and promyelocytes and eosinophil chemotaxis.

Pharmacology

Histamine Antagonists

All known H_1 histamine antagonists are actually inverse agonists. Currently, classification distinguishes between the older "first-generation" agents, which readily penetrate the blood–brain barrier and produce central nervous system effects, and the peripherally selective or "second-generation" H_1 antihistamines, which have a higher therapeutic index. Central effects of the first-generation H_1 antihistamines likely result from their interference with histamine function as a neurotransmitter. The first-generation H_1 antihistamines also bind to muscarinic and perhaps adrenergic receptors. Second-generation H_1 receptor antagonists are highly specific for peripheral rather than central H_1 receptors. They do not penetrate the CNS well and tend to have lower binding affinities for the cholinergic, α- and β-adrenergic receptor sites than do the first-generation antihistamines. Thus the relative incidence of anticholinergic and CNS adverse effects caused by second-generation H_1 antihistamines is similar to that produced by placebo. Table 50–1 describes properties of some common antihistamines.

TABLE 50–1. The Pharmacologic Characteristics of Antihistamine

Antihistamine	Anticholinergic Class	Sedation	Duration of Action (h)	Typical Adult Dose
Acrivastine	Alkylamine	+	6–8	8 mg tid
Azatadine	Piperidine	+	12	1–2 mg bid
Brompheniramine	Alkylamine	+ +	4–6	4 mg qid
Buclizine	Piperazine	+ +	4–6	50 mg bid
Carbinoxamine	Ethanolamine	+ + + +	3–6	4–8 mg qid
Cetirizine	Piperazine	+	12	5–10 mg qid
Chlorpheniramine	Alkylamine	+ +	4–6	4 mg qid
Clemastine	Ethanolamine	+ + + +	12–24	2 mg bid
Desloratadine	Piperidine	0	24	5 mg qd
Dexbrompheniramine	Alkylamine	+ +	12	3–12 mg bid
Dexchlorpheniramine	Alkylamine	+ +	3–6	4–6 mg tid
Dimenhydrinate	Ethanolamine	+ + + +	4–6	50–100 mg qid
Dimethindene	Alkylamine	+ +	8	1–2 mg tid
Diphenhydramine	Ethanolamine	+ + + +	4–6	25–50 mg qid
Doxylamine	Ethanolamine	+ + + +	6	7.5–12.5 mg qid
Fexofenadine	Piperidine	+	12	60 mg bid
Hydroxyzine	Piperazine	+ +	6–8	25 mg qid
Levocetirizine	Piperazine	0	24	5 mg qd
Loratadine	Piperidine	+	8–12	10 mg qd
Meclizine	Piperazine	+ +	6–8	25 mg tid
Pheniramine	Alkylamine	+ +	4–6	5–15 mg q4h
Phenyltoloxamine	Ethanolamine	+ + + +	4–8	7.5–25 mg tid
Promethazine	Phenothiazine	+ + + +	4–6	12.5–25 mg qid
Trimeprazine	Phenothiazine	+ + + +	4–6	2.5 mg qid
Tripelennamine	Ethylenediamine	+ + +	4–6	25–50 mg qid
Triprolidine	Alkylamine	+ +	4–6	2.5 mg qid

H_2 Receptor Antagonists

H_2 receptor antagonists are competitive inhibitors that have little effect outside the gastrointestinal tract. Their effectiveness results from inhibition of both acetylcholine stimulation of gastric acid secretion and the effects of gastrin.

Pharmacokinetics and Toxicokinetics

H_1 Receptor Antagonists

The antihistamines are generally well absorbed following oral administration and most achieve peak plasma concentrations within 2–3 hours. Dermal absorption is also consequential, especially with extensive or prolonged application to abnormal skin. The durations of action range from 3 hours to more than 24 hours. Hepatic metabolism is the primary route of metabolism for the antihistamines. Drug–drug interactions may be caused by modulation of cytochrome P450 (CYP) metabolism or interference with active transport mechanism (such as P-glycoprotein).

H_2 Receptor Antagonists

Cimetidine is the prototypical H_2 receptor antagonist. Cimetidine is rapidly and completely absorbed following oral administration. Cimetidine has a volume of distribution of approximately 2 L/kg with 13–25% protein binding. Up to 75% of cimetidine is eliminated unchanged in the urine, 15% is metabolized by the liver, and 10% is found unchanged in the stool. Cimetidine is responsible for numerous drug–drug interactions by inhibition of cytochrome P450 activity, as well as reduced hepatic blood flow. None of the other currently available H_2 receptor antagonists inhibit the cytochrome P450 oxidase system.

Clinical Manifestations

H_1 Receptor Antagonists

Although dry mouth and mydriasis are common adverse therapeutic effects, sedation is the most concerning. The clinical manifestations of H_1 receptor antagonist overdose are largely extensions of the adverse effects noted with therapeutic use of these agents. Following overdose with a first-generation H_1 antihistamine, patients typically present with CNS depression and an anticholinergic syndrome. Findings typically include mydriasis, tachycardia, fever, dry mucous membranes, urinary retention, diminished bowel sounds, and disorientation. Ingestion of second-generation antihistamines usually does not result in significant CNS depression or anticholinergic effects. As a result of sodium channel blockade following a large diphenhydramine overdose, prolongation of both the QRS complexes and QTc intervals may occur. Rhabdomyolysis can occur in patients with extreme agitation or seizures following an H_1 antihistamine overdose. Rhabdomyolysis is commonly noted in patients who overdose with doxylamine, even in the absence of trauma or any of the other common etiologies such as seizures, shock, or crush injuries.

H_2 Receptor Antagonists

Acute toxic effects appear to be extremely rare even following large (20 g) oral ingestions of H_2 receptor antagonists. Patients may develop tachycardia, dilated and sluggishly reactive pupils, slurred speech, and confusion.

Management

The patient's vital signs and mental status must be monitored. Patients should be attached to a cardiac monitor and observed for signs of sodium channel blockade (increased QRS duration), a prolonged QTc, dysrhythmias, and seizures. Assessment of the serum acetaminophen concentration is important because many antihistamine-containing cough and cold products include acetaminophen. Measurement of antihistamine concentrations is not readily available and is unnecessary for clinical assessment and management.

Gastrointestinal decontamination with oral activated charcoal is sufficient in most cases although orogastric lavage may be indicated in patients with massive overdose of a first-generation H_1 antihistamine. Serial assessments should be made of the patient's vital signs, particularly temperature, and mental status. Hypotension generally responds to 0.9% sodium chloride or lactated Ringer solution. If the desired increase in blood pressure is not attained, dopamine or norepinephrine may be titrated to achieve an acceptable blood pressure. In one instance, cardiogenic shock and myocardial depression resulting from a 10 g ingestion of

pyrilamine maleate could only be reversed with an intraaortic balloon counterpulsation device. Agitation, psychosis, or seizure generally responds readily to benzodiazepines or physostigmine (see Antidotes in Brief: Physostigmine). Cooling via evaporative methods is generally sufficient but severe hyperthermia may require submersion in an ice bath. Proper fluid management and urinary alkalinization are necessary to prevent myoglobin-induced nephrotoxicity.

The sodium channel blocking (type IA antidysrhythmic) properties of diphenhydramine may lead to wide complex dysrhythmias that resemble cyclic antidepressant overdose (Chaps. 61 and 71). Hypertonic sodium bicarbonate can reverse diphenhydramine-associated conduction abnormalities. Types IA, IC, and III antidysrhythmics are contraindicated.

Physostigmine can effectively reverse the peripheral or central anticholinergic syndrome if clinically indicated and was superior to benzodiazepines in one study. Contraindications to the use of physostigmine include a wide QRS complex and asthma. A dose of 1–2 mg in adults; 0.5 mg in children should be administered by *slow* intravenous infusion over 2–5 minutes with continuous monitoring of vital signs, breath sounds, and oxygen saturation by pulse oximetry. This initial dose may be repeated at 5–10-minute intervals if anticholinergic symptoms are not reversed and cholinergic symptoms such as salivation, diaphoresis, bradycardia, lacrimation, urination, or defecation do not develop. When improvement occurs as a result of physostigmine, it may be necessary to readminister the physostigmine at 30–60-minute intervals.

H_2 Receptor Antagonists

Patients who overdose on an H_2 antihistamine should receive 1 g/kg body weight of oral activated charcoal for potential coingestants if indicated.

DECONGESTANTS

History and Epidemiology

Decongestants are sympathomimetic medications that act on α-adrenergic receptors to produce vasoconstriction, to shrink swollen mucous membranes, and to improve bronchiolar air movement. Ephedrine, the first member of this class to be used pharmaceutically, is derived from *Ephedra* spp plants, and was used in China for at least 2000 years before it was introduced in Western medicine in 1924. Phenylephrine was introduced into clinical medicine in the 1930s. Several topical imidazoline decongestants have since been developed for clinical use. Recreational use of ephedrine-containing stimulants is common, and combinations containing these compounds with caffeine or other herbs may be marketed as "herbal ecstasy."

Pharmacology and Pharmacokinetics

Decongestants are pharmacologically active following topical or oral administration. Absorption from the gastrointestinal tract is rapid with peak blood concentrations occurring within 2–4 hours of ingestion. The decongestants phenylephrine, pseudoephedrine, ephedrine, and phenylpropanolamine reduce nasal congestion by stimulating the α-adrenergic receptor sites on vascular smooth muscle, which constricts dilated arterioles and reduces blood flow to engorged nasal vascular beds.

The imidazolines are generally reserved for topical application and are used for their local effects in the nasal passages and the eye. The more common medications include oxymetazoline hydrochloride, tetrahydrozoline hy-

drochloride, and naphazoline hydrochloride. Their vasoconstrictor effects are mediated by their actions as α-adrenergic agonists. In addition, these compounds show high affinity for imidazoline receptors, which are located in the ventrolateral medulla and some peripheral tissues. Stimulation of imidazoline receptors produces a sympatholytic effect with resultant bradycardia and hypotension. Oxymetazoline is the only compound with a duration of action greater than 8 hours; the other preparations average a duration of action of approximately 4 hours. The elimination half-lives of these drugs range from 2–4 hours.

Clinical Manifestations

Following a decongestant overdose, most patients will present with central nervous system stimulation, hypertension, tachycardia, or reflex bradycardia (in response to pure α-adrenergic agonist-induced hypertension). Headache was the most common initial symptom reported by patients who later developed severe toxicity. Hypertensive encephalopathy and intracranial hemorrhages are well described. Cardiovascular effects include myocardial infarction, bradycardia, atrial and ventricular dysrhythmias, and bowel ischemia.

When ingested the imidazoline decongestants are potent central and peripheral α_2-adrenergic and imidazoline receptor stimulants, and can cause central nervous system depression, hypotension, bradycardia, and respiratory depression. Children are particularly sensitive to these effects.

Management

Extreme agitation, seizures, tachycardia, hypertension, and psychosis should initially be treated with the administration of oxygen and intravenous benzodiazepines, expeditiously titrated upward to effect. A patient who remains hypertensive or has ischemic chest pain may be treated with phentolamine, an α-adrenergic antagonist, or nitroprusside, a venous and arterial vasodilator. A patient with a focal neurologic deficit or an abnormal neuropsychiatric examination should be evaluated for cerebral hemorrhage by a noncontrast head CT scan, and, if indicated, subsequent lumbar puncture.

A single dose of 1 g/kg body weight of activated charcoal is usually sufficient for decontamination unless a massive ingestion has occurred, at which point orogastric lavage may be performed.

Ventricular dysrhythmias from decongestant ingestions should be treated with standard doses of lidocaine or amiodarone. Phenylpropanolamine ingestions may cause hypertension, reflex bradycardia, and an atrioventricular block. Atropine must be used with caution because it can cause a dangerous increase in blood pressure as the reflex bradycardia is reversed. Therefore, a direct acting vasodilator such as phentolamine or nitroprusside is preferred, because by reversing the hypertension, the stimulus for the bradycardia is also corrected. Imidazoline-induced hypertension rarely requires therapy, but in the setting of symptomatic hypertension, a short-acting α-adrenergic antagonist such as phentolamine may be administered.

Physostigmine Salicylate

HISTORY

The history of physostigmine dates to antiquity and the Efik people of Old Calabar in Nigeria where the chiefs used the poisonous beans in a ritual to test the innocence or guilt of an accused person. Over the years, physostigmine, the active ingredient of these beans, was instrumental in the development of a bioassay for acetylcholine, concepts of neurohumoral transmission, mapping of cholinergic nerves, the concept of antagonism, the kinetics of enzyme inhibition, and an improved understanding of the blood–brain barrier.

CHEMISTRY AND AFFINITY FOR CHOLINESTERASE

Like acetylcholine, physostigmine is a substrate for the cholinesterases (choline ester hydrolases) erythrocyte acetylcholinesterase and plasma cholinesterase. Both acetylcholine and physostigmine bind to the cholinesterase enzymes to form a complex. Then a part of the substrate known as the leaving group, choline for acetylcholine, is removed, and the remaining acetylated (for acetylcholine) or carbamoylated (for physostigmine) enzyme is hydrolyzed, regenerating the enzyme and freeing the acetate or carbamate groups. For acetylcholine, the process is extremely quick, with a turnover time of 150 msec, whereas the half-life for hydrolysis of the carbamoylated enzyme is 15–30 minutes.

PHARMACOKINETICS

Physostigmine is poorly absorbed orally, with a bioavailability of less than 5–12%. Pharmacokinetic parameters following IV administration demonstrate the following: Vd 2.4 ± 0.6 L/kg; $t_{1/2}$ 16.4 ± 3.2 minutes; peak plasma concentration 3 ± 0.5 ng/mL; and clearance 0.1 L/min/kg. There is a 3-fold interindividual variability in plasma physostigmine concentrations. Plasma cholinesterase concentrations demonstrate inhibition within 2 minutes of initiating the physostigmine infusion; the half-life of plasma cholinesterase inhibition is 83.7 ± 5.2 minutes, with full recovery within 3 hours of the termination of the physostigmine infusion. Thus the effects on plasma cholinesterase inhibition last about 5 times longer than the half-life of physostigmine.

CLINICAL USE

Because of its ability to cause CNS arousal, physostigmine was used in the 1970s to reverse the CNS effects of a large number of anticholinergic xenobiotics appropriately as well as inappropriately to treat toxicity from nonanticholinergic xenobiotics. More than 600 xenobiotics were reported to respond to physostigmine. However, its major limitation was best defined when asystole was reported to follow physostigmine administration in patients with tricyclic antidepressant overdose. A reevaluation concluded that the risks of physostigmine use for xenobiotics that are not primarily antimuscarinic outweigh any benefit. In contrast, in the case of anticholinergic overdose, the use

of physostigmine is clearly beneficial. When compared with benzodiazepines, physostigmine was better at controlling agitation and reversing delirium, as well as shortening recovery time.

INDICATIONS

Indications for the use of physostigmine include the presence of peripheral or central anticholinergic manifestations without evidence of QRS or QTc prolongation. Peripheral anticholinergic manifestations include dry mucosa, dry skin, flushed face, mydriasis, hyperthermia, decreased bowel sounds, urinary retention, and tachycardia. Central anticholinergic manifestations include agitation, delirium, hallucinations, seizures, and coma. The relative contraindications to physostigmine use include reactive airways disease, peripheral vascular disease, intestinal or bladder obstruction, intraventricular conduction defects, and atrioventricular (AV) block.

ADVERSE EFFECTS

An excess of physostigmine results in the accumulation of acetylcholine at peripheral muscarinic receptors, and nicotinic receptors (skeletal muscle, autonomic ganglia, adrenal glands), as well as CNS sites. Muscarinic effects produce the stimulation of smooth muscle and glandular secretions in the respiratory, gastrointestinal, and genitourinary tracts, and the inhibition of contraction of most vascular smooth musculature. Nicotinic effects are stimulatory at low doses and depressant at high doses. For example, acetylcholine excess at the neuromuscular junction produces fasciculations followed by weakness and paralysis. The effect on the CNS results in anxiety, dizziness, tremors, confusion, ataxia, coma, and seizures. Patients overdosed with physostigmine should be managed with intravenous atropine titrated to reverse bronchial secretions and intensive supportive care including mechanical ventilation if needed.

DOSING

The dose of physostigmine is 1–2 mg in adults and 0.02 mg/kg (maximum: 0.5 mg) in children, intravenously infused over at least 5 minutes. The onset of action is usually within minutes. This dose can be repeated in 10–15 minutes if an adequate response is not achieved and muscarinic effects are not noted. Although a total of 4 mg in divided doses is usually sufficient in most clinical situations, significant interindividual variability exists. Rapid administration may cause bradycardia, hypersalivation leading to respiratory difficulty, and possibly seizures. Atropine should be at the bedside and should be titrated to effect should excessive cholinergic toxicity develop. A dose of atropine administered at one-half the physostigmine dose is often recommended.

AVAILABILITY

Physostigmine is available as Antilirium in 2-mL ampules with each milliliter containing 1 mg of physostigmine salicylate. The vehicle contains sodium bisulfite and benzyl alcohol.

51 Antimigraine Medications

A migraine headache is a neurovascular disorder often initiated by a trigger and characterized by a headache, which may be associated with an aura, and a variety of organ system complaints, such as visual disturbances, allodynia, nausea, and urinary frequency. Abortive therapy and prophylactic therapy ideally target these processes (Table 51–1).

Although ergots were formerly the mainstay of therapy for treatment of migraines, with the advent of the triptans, this class of medications has essentially replaced the ergots.

ERGOT ALKALOIDS

History and Epidemiology

Ergot is the product of *Claviceps purpurea*, a fungus that contaminates rye and other grains. This fungus can elaborate diverse substances, including ergotamine, histamine, tyramine, isomylamine, acetylcholine, and acetaldehyde. In 600 B.C., an Assyrian tablet made mention of contamination of grain believed to be by *Claviceps purpurea*. In approximately 400 B.C., a contaminated grass that killed pregnant women was described. In the Middle Ages, epidemics causing gangrene of the extremities, with mummification of limbs, were depicted in the literature. The disease was called holy fire or St. Anthony's fire because of the blackened limbs resembling the charring from fire and the burning sensation expressed by its victims. Abortion and seizures were also reported with this poisoning. As early as 1582, midwives used ergot to assist in the childbirth process. Since 1950, the clinical use of ergot derivatives is almost entirely limited to the treatment of vascular headaches. Ergonovine, another ergot derivative, is used in obstetric care for its stimulant effect on uterine smooth muscle. Methylergonovine is used for postpartum uterine atony and hemorrhage. Ergot derivatives have also been used as "cognition enhancers" to help manage orthostatic hypotension and to prevent the secretion of prolactin.

Pharmacology and Pharmacokinetics

The ergot alkaloids can be divided into three groups: amino acid alkaloids, dihydrogenated amino acid alkaloids, and amine alkaloids. The pharmacokinetics of the ergot alkaloids are well defined from controlled human volunteer studies, whereas the toxicokinetics are essentially unknown (Table 51–2). The pharmacologic effects of the ergot alkaloids can be subdivided into central and peripheral effects (Table 51–3). In the CNS, ergotamine stimulates serotonergic (tryptaminergic) receptors, potentiates serotonergic effects, blocks neuronal serotonin reuptake, and has central sympatholytic actions. Peripherally, ergotamine acts as a partial α-adrenergic agonist or as an antagonist at adrenergic, dopaminergic, and serotonergic (tryptaminergic) receptors. There may also be a direct vasoconstrictive effect on the media of the arterioles.

Clinical Manifestations

Ergotism, a toxicologic syndrome resulting from excessive use of ergot alkaloids, is characterized by intense burning of the extremities, hemorrhagic vesic-

TABLE 51–1. Xenobiotics Used for Migraine Treatment

Prophylactic	Abortive
Angiotensin II receptor blockers	Acetaminophen
β-Adrenergic antagonists	Antiemetics
Botulinum toxin A (Botox A)	Aspirin
Butterbur root	Butalbital
Calcium channel blockers	Caffeine
Coenzyme Q10	Corticosteroids
Feverfew	Ergots
Flunarizine	Lidocaine (intranasal)
Gabapentin	Magnesium (IV)
Lamotrigine	Midrin (isometheptene/dichloral-phenazone/acetaminophen)
Levetiracetam	
Magnesium (oral)	NSAIDs
Monoamine oxidase inhibitors	Opioids
Pizotifen	Oxygen
Riboflavin	Sedative-hypnotics
Selective serotonin reuptake inhibitors	Triptans
	Valproic acid (intravenous)
Topiramate	
Tricyclic antidepressants	
Valproic acid	

Prophylactic xenobiotics usually are taken to prevent triggering of migraines, and abortive xenobiotics usually are taken to stop the clinical manifestations of migraines once they are triggered. However, the separation between the two groups is not strict, and xenobiotics can be used in both roles.

ulations, pruritus, formications, nausea, vomiting, and gangrene (Table 51–4). Headache, fixed miosis, hallucinations, delirium, cerebrovascular ischemia, infarction and convulsions are also associated with ergotism and has been called "convulsive" ergotism. Chronic ergotism usually presents with peripheral ischemia of the lower extremities, although ischemia of cerebral, mesenteric, coronary, and renal vascular beds is well documented.

Ergotaminism is a syndrome caused specifically by ergotamine use. Symptoms of vascular insufficiency such as cold extremities, extremity pain at rest,

TABLE 51–2. Pharmacokinetics of Ergot Derivatives

Medication	$t_{1/2}$ (hours)	Duration of Action (hours)	Bioavailability (%)	Metabolism/ Elimination
Ergotamine	2 (1.4–6.2)	22 (IV)	100 (IV) 47 (IM) <5 (P0)	Liver Bile excretion
Dihydroergotamine	2.4	3–4 (IM)	100 (IM) 40 (nasal) <5 (PO)	Liver Bile excretion
Ergonovine	1.9	3	—	Liver
Methylergonovine	1.4–2	3	78 (IM) 60 (PO)	Liver
Methysergide	1 (PO)	—	13 (PO)	Liver (metabolized to methylergonovine)

TABLE 51–3. Pharmacology of Ergot Derivatives

Compound	Interactions with Tryptaminergic (Serotonergic) Receptors	Interactions with Dopaminergic Receptors	Interactions with α-Adrenergic Receptors
Ergotamine (amino acid alkaloid)	Vasculature: partial agonist Smooth muscles: nonselective antagonist CNS: poor agonist/antagonist	CNS: Emetic (potent)	Vasculature: partial agonist/antagonist Smooth muscles: partial agonist/antagonist CNS: antagonist PNS: antagonist
Bromocriptine (amino acid alkaloid)	Weak antagonist	CNS: partial agonist/antagonist; inhibits prolactin secretion; emetic (mild)	Vasculature: antagonist
Dihydroergotamine (dihydrogenated group)	Smooth muscles: partial agonist/antagonist CNS: agonist lateral geniculate nucleus	CNS: emetic (mild) Sympathetic ganglia: antagonism	Vasculature: Partial agonist (veins); antagonist (arteries) Smooth muscles: antagonist CNS/PNS: antagonist
Ergonovine and methyl ergonovine (amine alkaloid)	Smooth muscles: potent antagonist Vasculature: agonist in umbilical and placental vessels CNS: partial antagonist/agonist	CNS: emetic (mild); inhibits prolactin (weak); partial agonist/antagonist Vasculature: weak antagonist	Vasculature: partial agonist
Methysergide (amine alkaloid)	Vasculature: partial agonist CNS: potent antagonist	None	None

Adapted with permission from Peroutka SJ: Drugs effective in the therapy of migraine. In: Hardman JG, Limbird LE, Molinoff PB, et al, eds: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York. McGraw-Hill, 1996, pp. 491–496.

TABLE 51–4. Clinical Manifestations of Ergotism

Central effects	Peripheral effects
Agitation	Bradycardia
Cerebrovascular Ischemia	Hypertension
Hallucinations	
Headaches	**Ischemic effects**
Miosis (fixed)	Angina
Nausea	Cerebral infarction
Seizures	Gangrene
Twitching (facial)	Hemorrhagic vesiculations and skin bullae
Vomiting	Mesenteric infarction
	Myocardial infarction
	Renal infarction

numbness, cyanosis, and intermittent claudication are most commonly reported. CNS manifestations rarely occur in ergotaminism. Although restlessness, nausea, vomiting, or agitation develops within 4 hours of an acute overdose, peripheral vasospasm may not be obvious for 24 hours.

Vascular angiography demonstrates distal, segmental vessel spasm with increased collateralization in patients with chronic ergotism. The coronary, renal, cerebral, ophthalmic, and mesenteric vasculature, as well as the vessels of the extremities, may also be affected. Bradycardia is believed to be a reflex baroreceptor-mediated phenomenon associated with vasoconstriction, but a reduction in sympathetic tone, direct myocardial depression, and increased vagal activity may also be factors.

Treatment

The treatment for a patient with ergot alkaloid toxicity depends on the nature of the clinical findings. Gastric emptying should rarely be used, if at all, because vomiting is a common early occurrence and the ingestion may be complicated by seizure activity. Activated charcoal should be administered shortly after an acute oral overdose. If emesis is present, metoclopramide or a 5-HT_3 antagonist, such as ondansetron, can be used as an antiemetic to facilitate the administration of activated charcoal. In mild cases characterized by minimal pain of the extremities, supportive measures such as hydration and analgesia are all that are needed. With more serious vascular compromise, intravenous vasodilators, such as sodium nitroprusside, nitroglycerin, and phentolamine, are indicated to reverse the ischemia. Prazosin, captopril, and nifedipine have also been used in cases with mild signs and symptoms of vasospasm. Heparin, corticosteroids, or low-molecular-weight dextran may prevent sludging and clot formation. Arteriotomy may be necessary to remove large clots. Benzodiazepines should be used to treat seizures or hallucinations.

TRIPTANS

Currently available triptans include naratriptan, sumatriptan, zolmitriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan (Table 51–5).

Pharmacology

Triptans are all primarily 5-HT_{1B} and 5-HT_{1D} receptor agonists and have less activity at 5-HT_{1A} and 5-HT_{1F} receptors. The triptans also inhibit dural neurogenic inflammation by preventing the release of vasodilating neuropeptides

TABLE 51–5. Pharmacokinetics of Triptans

Medication	$t_{1/2}$ (hours)	Duration of Action (hours)	Lipophilicity	Bioavailability (%)	Metabolism/Elimination
Sumatriptan	2–2.5	4	Low	14 (P0); 96 (SQ)	MAO-A
Almotriptan	3–3.7	24	Unknown	70–80	CYP3A4, CYP2D6 (PO), MAO-A (minor)
Eletriptan	3.6–6.9	14–16	High	50	CYP3A4
Frovatriptan	25	24	Low	24–30	CYP1A2 renal elimination
Naratriptan	4.5–6.6	Unknown	High	63–74	Renal (major) CYP
Rizatriptan	1.8–3	25	Moderate	40–45	MAO-A
Zolmitriptan	1.5–3.6	18	Moderate	40–49	CYP1A2, MAO-A (minor)

from peripheral trigeminal nerves. Peripherally, triptans cause vasospasm systemically through the 5-HT_{1B} receptor. The available triptans are pharmacodynamically similar but differ with regard to the pharmacokinetics (Table 51–5).

Clinical Manifestations

With appropriate therapeutic use, the adverse effects associated with the triptans are minimal and include nausea, vomiting, dyspepsia, flushing, and paresthesia. However, the most consequential adverse effects are related to vasospasm. Chest pressure symptoms are reported in up to 15% of sumatriptan users. Although these chest pressure symptoms are usually not secondary to cardiac ischemia in origin, myocardial ischemia and infarction are well described. Chest pain that is not cardiac in origin may result from esophageal spasm. Renal infarctions (Fig. 51–1) and ischemic colitis are also described. Other rare reports describe transient ischemic attacks and cerebral vascular hemorrhage and infarctions.

Treatment

Treatment of triptan-induced vasospasm is dependent on the route of exposure and the organ system affected. Decontamination is not feasible after subcutaneous exposures, but can be effective in overdoses of oral preparations. A single dose of activated charcoal should be sufficient for most cases; orogastric lavage is probably unnecessary.

Triptan-induced vasoconstriction and ischemia should be reversed with a calcium channel blocker or intravenous vasodilators, such as sodium nitroprusside or nitroglycerin, or by the α-adrenergic antagonist phentolamine.

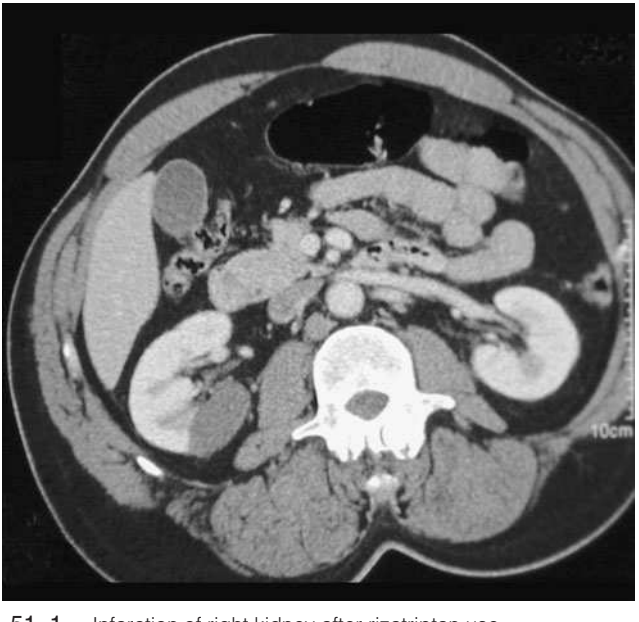

FIG. 51–1. Infarction of right kidney after rizatriptan use.

Cases of sumatriptan-associated myocardial infarction are treated with aspirin, heparin, morphine, and intravenous nitroglycerin as needed.

ISOMETHEPTENE

Isometheptene is a mild vasoconstrictor marketed as a combination preparation (Midrin) that includes dichloralphenazone, a muscle relaxant, and acetaminophen. It has indirect α- and β-adrenergic agonist effects, as well as minor direct α-adrenergic agonist effects on the peripheral vasculature. Cerebral vasoconstriction is reported after excessive isometheptene and sumatriptan usage, as well as therapeutic isometheptene usage. Treatment of isometheptene-induced vasoconstriction should include discontinuation of the medication and reversal of the vasoconstriction with calcium channel blockers or vasodilators, such as sodium nitroprusside, nitroglycerin, or phentolamine.

52 Antineoplastics

Overdoses of antineoplastic medications are infrequent; however, these events are of greater consequence than overdoses of many other medications because of their narrow therapeutic index. A review of the 2819 orders for cytotoxic medications at a pharmacy satellite showed that 93 orders (3%) contained at least 1 error in the dosage regimen—3 of the errors in dosage regimen were classified as potentially lethal, 13 as serious, 5 as significant, and 72 as minor. Most antineoplastic medications can be grouped into one of these 4 categories: alkylating agents, antimetabolites, antimitotics, and antibiotics (Table 52–1).

METHOTREXATE

Pharmacology

Methotrexate (MTX) is an important therapy for a variety of cancers; its immunosuppressive activity allows it to also be used for rheumatoid arthritis, organ transplantation, psoriasis, trophoblastic diseases, and therapeutic abortion. Its therapeutic and toxic effects are based on its ability to limit DNA and RNA synthesis by inhibiting dihydrofolate reductase (DHFR) and thymidylate synthetase (Fig. 52–1). This inhibition stops reduced folate production, which is necessary for nucleotide formation and DNA/RNA synthesis. The bioavailability of MTX appears to be limited by a saturable intestinal absorption mechanism. At oral doses less than 30 mg/m^2, the absorption is 90%; at doses greater than 80 mg/m^2, the absorption is less than 10–20%. Conventional intravenous doses of up to 100 mg/m^2 can be administered without leucovorin rescue. Doses of 1000 mg/m^2 are considered potentially lethal. Much higher doses (2–3 g/m^2) can be given when MTX is followed by leucovorin to prevent life-threatening toxicity. MTX is excreted unchanged in the urine by both glomerular filtration and active tubular secretion.

Clinical Manifestations

The clinical manifestations of MTX toxicity include stomatitis, esophagitis, renal failure, myelosuppression, hepatitis, and central neurologic system dysfunction. Commonly observed signs include increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (81%), nausea and vomiting (66%), mucositis (33%), dermatitis (18%), leukopenia (11%), thrombocytopenia (9%), and creatinine elevation (7%).

Nausea and vomiting typically begin 2–4 hours after high-dose therapy (>1000 mg/m^2) and last for about 6–12 hours. Mucositis, characterized by mouth soreness, stomatitis, or diarrhea, usually occurs 1–2 weeks after therapy and can last for 4–7 days. Pancytopenia usually occurs within the first 2 weeks after an acute exposure. The neurologic complications associated with either high-dose systemic MTX therapy or intrathecal administration are the most consequential manifestations. The manifestations usually occur from hours to days after the initiation of therapy and include hemiparesis, paraparesis, tetraparesis, seizures, and dysreflexia. Clinical findings occurring within several hours (usually within 12 hours) of therapy are attributed to chemical arachnoiditis, and they include acute onset of fever, meningismus, pleocytosis, and increased cerebrospinal fluid (CSF) protein concentration.

TABLE 52–1. Classification of Antineoplastics and Their Effects

Class	Antineoplastic	Adverse Effects
Alkylating	Busulphan	Hyperpigmentation, pulmonary fibrosis, hyperuricemia
	Dacarbazine	Hypotension, hepatocellular toxicity, influenzalike syndrome
	Melphalan	Pulmonary fibrosis
	Mustards	
	Chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine	Hemorrhagic cystitis, encephalopathy, pulmonary fibrosis
	Nitrosourea	
	Carmustine, lomustine, semustine	Pulmonary fibrosis, hepatocellular toxicity, renal insufficiency
	Platinoids	
	Cisplatin	Renal failure, peripheral neuropathy, hypomagnesemia, hypocalcemia, hyponatremia, ototoxicity
	Carboplatin, iproplatin	Myelosuppression, hypomagnesemia, hypocalcemia, hyponatremia
	Procarbazine	MAOI activity
Antimetabolite	Methotrexate	Mucositis, nausea, diarrhea, hepatocellular toxicity
	Purine analogs	
	Fludarabine	Encephalopathy, muscle weakness
	Mercaptopurine	Hyperuricemia, pancreatitis,
	Pentostatin	Hepatocellular toxicity cholestasis
	Thioguanine	Hyperuricemia
	Pyrimidine analogs	
	Cytarabine	Acute lung injury, neuropathy, cerebellar ataxia
	Fluorouracil	Cardiogenic shock, cardiomyopathy, neuropathy, cerebellar ataxia
Antimitotic	Epipodophyllotoxin	
	Etoposide, teniposide	CHF, hypotension
	Paclitaxel	GI perforation, peripheral neuropathy, dysrhythmias
	Vinca alkaloids	
	Vinblastine, vincristine, vindesine	Peripheral neuropathy, hyponatremia
Antibiotics	Anthracycline	
	Daunorubicin, doxorubicin, epirubicin, idarubicin	Congestive cardiomyopathy
	Bleomycin	Pulmonary fibrosis
	Dactinomycin	Hepatocellular toxicity
	Mithramycin	Flush
	Mitomycin C	Hemolytic uremic syndrome
	Mitoxantrone	Congestive cardiomyopathy
Enzyme	L-Asparaginase	Hypersensitivity, pancreatitis

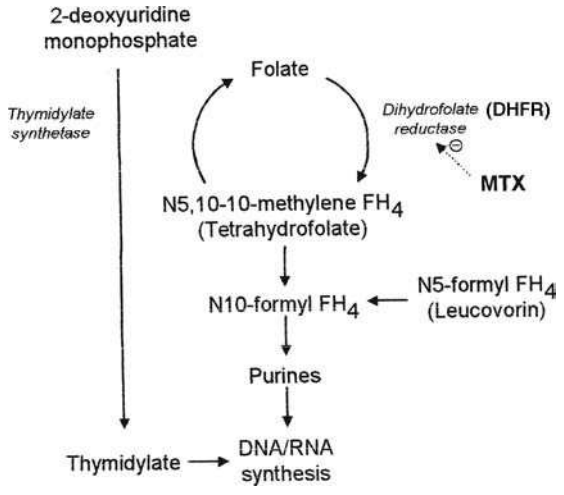

FIG. 52–1. Mechanism of methotrexate (MTX) toxicity. MTX inhibits dihydrofolate reductase (DHFR) activity, which is necessary for DNA and RNA synthesis. Leucovorin bypasses blockade to allow for continued synthesis.

Management

Activated charcoal adsorbs MTX and should be administered as soon as possible following oral overdose to limit drug absorption. Multiple-dose activated charcoal and cholestyramine can significantly decrease the elimination half-life of MTX by interrupting the enterohepatic circulation. This can also increase the clearance of parenterally administered MTX, but is most beneficial when renal clearance is diminished. Adequate hydration and urinary alkalinization with IV sodium bicarbonate (to urine pH 7–8) (see Antidotes in Brief: Sodium Bicarbonate) are also important to prevent renal failure in patients who receive inadvertent high doses. A complete blood cell count (CBC) should be done on days 7, 10, and 14 because life-threatening complications, such as bleeding disorders and overwhelming sepsis, can occur.

Leucovorin (folinic acid) (*N*-5-formyl-tetrahydrofolate) significantly limits bone marrow and gastrointestinal toxicity. Leucovorin is most beneficial when administered within 1 hour of exposure but should still be given to all patients after an excessive exposure. Although dosing regimens exist for MTX chemotherapy, following overdose all patients should be given 100 mg/m^2 intravenously every 3–6 hours (Antidotes in Brief: Leucovorin [Folinic Acid] and Folic Acid). Serum MTX concentrations should be monitored and leucovorin therapy continued until the concentration is below 0.01 μmol/L (1×10^{-8} mol/L). In patients with marrow toxicity, leucovorin therapy should be continued until marrow recovery, even if serum MTX is no longer detectable.

Carboxypeptidase G_2 ($CPDG_2$) is a rescue agent that inactivates MTX by cleaving its terminal glutamate group. Following $CPDG_2$ administration, serum MTX concentration decreases within 1 hour. $CPDG_2$ is available for compassionate use (protocol No. NCI 92-C-0134) by patients with a high serum MTX concentration (at least 10 μmol/L more than 42 hours after initia-

tion of MTX therapy) or under investigational protocol (NCI 92-C-0137) for intrathecal (IT) overdoses (≥100 mg IT MTX) from the National Cancer Institute (e-mail: ncicssc@mail.nih.gov; tel: 888-624-1937 or 301-496-5725; fax: 301-881-8239). Leucovorin and thymidine treatments are continued during $CPDG_2$ use because this enzyme does not enter the cell. The investigational dose for $CPDG_2$ is 50 units/kg IV and repeat administration may be necessary if the MTX concentration remains greater than 1 μmol/L.

Thymidine has also been used to rescue cells from the cytotoxic effects of MTX. It is currently available under an investigational protocol (NCI 92-C-0134) for use by patients with high serum MTX concentrations, severe manifestations of toxicity (ie, mucositis, thrombocytopenia, neutropenia, and hepatic insufficiency), and renal insufficiency, from the National Cancer Institute (e-mail: ncicssc@mail.nih.gov; tel: 888-624-1937 or 301-496-5725; fax: 301-881-8239). The investigational dose for thymidine is 8 g/m^2/d IV, and this treatment is used in conjunction with leucovorin and carboxypeptidase.

Charcoal hemoperfusion removed more than 50% of MTX in 4 patients with impaired renal MTX clearance during high-dose MTX therapy. Because in vitro studies indicate that the toxic effects of 100 μmol/L of MTX cannot be reversed by 1000 μmol/L of leucovorin, this suggests that hemoperfusion should be used to lower persistent MTX plasma concentrations of greater than 100 μmol/L. Acute intermittent hemodialysis with a high-flux dialyzer membrane yields an effective mean plasma MTX clearance that closely approximates normal renal MTX clearance and should be considered if it is available. Thus, patients at greatest risk for developing MTX toxicity despite leucovorin treatment should be considered for extracorporeal elimination because they are most likely to benefit from this procedure. Although hemoperfusion is preferred over hemodialysis, the latter can be used if it is the only choice available and can offer the additional benefit of correcting fluid and electrolyte disorders resulting from renal failure.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) should be considered in patients with MTX overdose and pancytopenia. The dose is 5 μg/kg/d IV or subcutaneously (SC) and it is continued beyond the expected white blood cell (WBC) nadir.

VINCRISTINE AND VINBLASTINE

Pharmacology

Vincristine and vinblastine are used for the treatment of leukemias, lymphomas, and certain solid tumors. Their mechanism of activity is similar to that of colchicine, podophyllotoxin, and the taxoids (eg, paclitaxel, docetaxel). These agents disrupt microtubule assembly from tubulin subunits by either preventing their formation or depolymerization, both of which are necessary for routine cell maintenance and division.

Vincristine overdose is the most frequently reported antineoplastic overdose in the literature. This is because there are at least 4 different ways to misdose this drug, including confusing it with vinblastine, misinterpreting the dose, administering by the wrong route, and confusing 2 different-strength vials.

Clinical Manifestations

Vincristine produces less bone marrow suppression and more neurotoxicity than vinblastine. The fall in cell counts begins within the first week and may

last for up to 3 weeks. Other manifestations of acute vincristine toxicity are mucositis, CNS disorders, and the syndrome of inappropriate antidiuretic hormone (SIADH). Autonomic dysfunction is observed, and it commonly includes ileus, constipation, and abdominal pain. Atony of the bladder, hypertension, and hypotension can occur as well. Ascending peripheral neuropathies also occur during vincristine therapy. A loss of reflexes, the earliest and most consistent sign of vincristine neuropathy, is maximal at 17 days after a single massive dose.

Management

Patients receiving an inadvertent amount of an IV dose of vincristine should be admitted to a cardiac-monitored bed and observed for 24–72 hours. Seizures, dysrhythmias, and alterations in blood pressure can be expectantly managed, although prophylactic phenobarbital and benzodiazepine have been used. Calcium channel blockers (nifedipine and amlodipine) will control hypertension. Blood counts must be monitored daily, and granulocyte colony-stimulating factor (G-CSF) may be used to treat neutropenia.

If patients remain asymptomatic during the observation period, they can be discharged with followup for bone marrow suppression and SIADH. The symptoms of acute toxicity usually last for 3–7 days, and the neurologic sequelae may last for months before some resolution is observed. Glutamic acid, 500 mg orally 3 times a day, decreases loss of Achilles tendon reflex and paresthesia. Leucovorin may also shorten the course of vincristine-induced peripheral neuropathy and myelosuppression.

Enhanced Elimination

There is no evidence demonstrating the efficacy of multiple-dose activated charcoal to enhance the elimination of vincristine. Double-volume exchange transfusion was successful in 2 children. Similarly, plasmapheresis may have some role in adults.

ANTHRACYCLINES

Pharmacology

The antineoplastics derived from the bacterium *Streptomyces* are dactinomycin, daunorubicin, doxorubicin, bleomycin, mitomycin, and plicamycin. Daunorubicin and doxorubicin share many common indications for cancer therapy, but they differ as doxorubicin is used for solid tumors such as breast carcinoma. The mechanism of therapeutic action of the anthracyclines is attributed to DNA intercalation and activation of topoisomerase II.

Cardiotoxicity, which is believed to result from free radical formation, limits the therapeutic use of anthracyclines.

Clinical Manifestations

The cardiotoxic manifestations can be divided into acute and chronic categories. The various findings described with acute toxicity include dysrhythmias, ST and T-wave changes on the ECG, diminished ejection fraction that usually resolves over 24 hours, and sudden death. Acute pericarditis and myocarditis resulting in conduction defects and congestive heart failure are also reported. In cumulative doses, the anthracycline antibiotics cause a cardiomyopathy

that results in congestive heart failure. The condition is irreversible and is associated with a 48% mortality.

Myelosuppression and mucositis are other effects associated with the use of the anthracycline agents. They typically occur within 1–2 weeks and patients recover. The white cells are affected more than either the red cells or platelets. Patients with diminished drug clearance (eg, liver failure) are at risk for the development of these findings.

Four cases of mitoxantrone overdose are reported in the literature. Following 10-fold errors in dosing (100 mg/m^2 instead of 10 mg/m^2), early onset of nausea with vomiting and myelosuppression with fever occurred. Acute decreased cardiac contractility was observed by echocardiography in 1 patient who was asymptomatic. Three patients developed fatal congestive heart failure (CHF) from 1–4 months later.

Management

Because there are no specific antidotes for this class of agents, management is largely supportive. Monitoring for cardiotoxicity and pancytopenia is necessary. A baseline chest radiograph, electrocardiogram, troponin, and left-ventricular ejection fraction (at rest and/or with stress) are required. Although digoxin and furosemide should be used to manage acute CHF, a variable response can be expected.

Dexrazoxane is a cardioprotectant that limits the effects of doxorubicin by chelating intracellular iron, which mediates the formation of free radical cellular damage. In clinical trials, patients receiving dexrazoxane had smaller decreases in left ejection fraction per dose of doxorubicin and fewer histologic changes on cardiac biopsy. The current role of this chelator is in limiting cardiotoxicity in patients receiving greater than 300 mg/m^2 of doxorubicin. Other cardioprotectants under investigation include amifostine and monohydroxyethylrutoside.

Enhanced Elimination

The anthracycline agents are highly protein bound and have a large volume of distribution, which make them unlikely candidates for hemodialysis. However, the early institution of hemoperfusion may enhance elimination.

NITROGEN MUSTARDS

Pharmacology

The nitrogen mustards are cyclophosphamide, ifosfamide, chlorambucil, mechlorethamine, and melphalan. Their indicated uses include immunosuppression (eg, controlling graft-versus-host rejection, collagen vascular diseases) and chemotherapy. The tumoricidal activity of these agents is the result of the formation of reactive intermediates that bind to nucleophilic moieties on the DNA chain, which inactivates DNA synthesis.

Clinical Manifestations

Chlorambucil and ifosfamide can produce altered mental status and seizures from therapeutic use or from an overdose. Both compounds produce chloroacetaldehyde, which is purported to be a nervous system toxin. Seizures are more commonly associated with chlorambucil and typically occur within 6

hours, may appear as generalized tonic-clonic activity or staring spells, and can last for 24 hours. Myelosuppression occurs in patients with both acute and chronic overdoses and can present as late as 41 days postexposure. Recovery is expected within 1 week of the nadir, and G-CSF treatment may be necessary. Cyclophosphamide and its analog ifosfamide induce hemorrhagic cystitis from their irritating metabolite, acrolein.

In the overdose setting, cyclophosphamide can cause dysrhythmias, myocardial necrosis, and death. ECG changes are noted at doses of 120 mg/kg and heart failure and myocarditis at doses greater than 150 mg/kg. The onset of heart failure can be sudden, and patients older than 50 years of age, and those with prior treatment with anthracyclines, are at greatest risk for cardiac toxicity.

Management

Recommendations for patients with an acute chlorambucil exposure include routine gastrointestinal decontamination, a 6-hour observation, a baseline CBC and hepatic enzymes, and a followup CBC weekly for 4 weeks. Ifosfamide-induced encephalopathy can be managed with methylene blue (50 mg IV as a 1% solution). Seizures were reported to be more effectively managed with benzodiazepines and barbiturates than with phenytoin. When gross hematuria from cyclophosphamide or ifosfamide therapy persists, treatments reported to be effective include electrocauterization, systemic vasopressin, and intravesical administration of silver nitrate, formalin, prostaglandin $F_{2\alpha}$, and hydrostatic pressure. Some of the preventive therapies that seem to reduce this occurrence include adequate hydration for dilution effect, frequent bladder emptying, IV administration of sodium 2-mercaptoethanesulfonate (MESNA), and intravesical *N*-acetylcysteine. The IV dose of MESNA is 20% of the cyclophosphamide or ifosfamide amount (wt/wt) to be administered during therapy and again at 4 and 8 hours.

PLATINOIDS

Pharmacology

The platinum-containing compounds include cisplatin, carboplatin, and oxaliplatin. These agents bind to DNA to form inter- and intrastrand bonds, which lead to DNA dysfunction and strand breakage. These agents are eliminated from the body primarily in the urine and at varying rates. Patients with decreased creatinine clearance (<30 mg/m^2) have prolonged elimination half-lives of platinoids.

Clinical Manifestations

The more common manifestations of toxicity with cisplatin therapy are renal dysfunction, auditory impairment, and peripheral sensory neuropathy. Myelosuppression is a dose-limiting factor for carboplatin and iproplatin, which does not occur with cisplatin. The marrow effects are delayed, with nadir occurring 3–5 weeks after the start of therapy. Other manifestations of overdose involve neurologic, visual, hearing, bone marrow, pancreatic, and renal disorders. The most common renal disorder is irreversible distal tubular necrosis. Hyponatremia is an uncommon finding with cisplatin exposure and is attributed to either sodium wasting nephropathy from renal tubular dysfunction or SIADH. At doses greater than 200 mg/m^2, the development of seizures, encephalopathy,

and irreversible peripheral sensory neuropathy is of concern. At this dose, visual impairment may occur within the first week of exposure. This can include temporary visual loss with permanent loss of color discrimination. High-frequency (>2000 Hz) hearing loss is evident 2–3 days after exposure to doses greater than 500 mg/m^2.

Management

Renal protection and enhanced elimination of platinum are the two primary goals in the management of a cisplatin overdose. Sodium chloride diuresis both promotes the inactive anionic state of cisplatin and decreases the urine platinum concentration to limit nephrotoxicity during therapy. Hydration with 0.9% NaCl solution and an osmotic diuretic (eg, mannitol) should be administered to achieve a high urine output (eg, 1–3 mL/kg/h) for 6–24 hours postexposure. Amifostine and sodium thiosulfate are effective nephroprotectants. Thiosulfate is given as an IV bolus of 4 g/m^2 followed by infusion of 12 g/m^2 over 6 hours. The use of thiosulfate is limited because it must be administered within 1–2 hours after exposure.

Hemodialysis is ineffective in patients with cisplatin overdoses, likely as a result of this agent's high protein binding. However, in patients with renal failure, hemodialysis may be beneficial. Plasmapheresis was reported to be beneficial.

INTRATHECAL OVERDOSE

Intrathecal overdoses with vincristine, methotrexate, doxorubicin, daunorubicin, and cytarabine are reported in the literature. Common sources of error are confusing the IV for the intrathecal agent and misidentifying the strength of the solution vial in the preparation of the medication. Removal of as much of the agent as possible is the patient's only chance of having an acceptable prognosis. Upon recognition of the occurrence, the patient must be placed in the upright position, which significantly delays the flow of an intralumbar administered agent to the cerebral ventricles. The lumbar puncture site must be maintained or reestablished so that as much of the CSF can be drained as possible. CSF drainage can be accomplished in short time intervals, considering that CSF production is 30 mL/h. CSF exchange should be accomplished by lavaging the intrathecal space with lactated Ringer solution. An equal volume of the CSF space should be used in each pass of the lavage, and 2–3 passes should be performed to complete the procedure. The volume of CSF in a child older than 3 years of age approaches that of an adult (ie, 120 mL). For large exposures, CSF perfusion must follow. This is performed by passing solution through a ventriculostomy and out a lumbar drainage catheter. Lactated Ringer solution with 15–25 mL of fresh-frozen plasma added per liter of crystalloid is infused at 150 mL/h for 18–24 hours.

Additional therapies for vincristine overdose can include glutamic acid (10 g IV over 24 hours, then 500 mg orally 3 times a day), leucovorin (25 mg IV every 6 hours), and pyridoxine (50 mg IV every 8 hours). These agents are continued for 1 week or until the neurologic symptoms stabilize. Dexamethasone (4 mg/m^2 IV every 6 hours) may be given for meningeal inflammation.

Intrathecal overdoses of MTX commonly occur because a more concentrated solution vial is mistaken for one that is less concentrated. The neurotoxicity associated with these events includes chemical arachnoiditis, ascending neuropathy, encephalopathy, and seizures. The seizures can be treated

with phenobarbital and/or benzodiazepines. CSF removal of MTX is crucial, and for amounts less than 100 mg CSF drainage may be adequate if performed within 30–60 minutes of administration. When a longer period of time has elapsed, or a larger amount is involved, CSF exchange is necessary, and possibly CSF perfusion as well. CSF decontamination should continue until the final CSF MTX concentration is about 100 μmol/L, which is a peak therapeutic level for a 12-mg intrathecal MTX dose. Although there are no reports of myelosuppression resulting from such an event, IV leucovorin is indicated. High-dose leucovorin rescue should be started upon recognition of the overdose. Leucovorin is *not* to be administered intrathecally because seizures and death can occur. Additional therapies are hydration and urinary alkalinization to prevent renal toxicity, and IV dexamethasone to lessen meningeal inflammation. Intrathecal $CPDG_2$ dramatically shortens the MTX CSF half-life.

EXTRAVASATIONAL INJURY

Extravasational injuries are among the most consequential local toxic events. When an antineoplastic agent leaks into the perivascular space, significant necrosis of skin, muscles, and tendons can occur, with resultant loss of function. The initial manifestations may include swelling, pain, and a burning sensation that can last for hours. Days later, the area becomes erythematous and indurated, and can either resolve or proceed to ulceration and necrosis.

These inadvertent events appear to be about 50 times more frequent in the hands of an inexperienced clinician, and several factors are associated with extravasational injuries, including (a) patients with poor vessel integrity and blood flow, such as the elderly, those who undergo numerous venipunctures, and radiation therapy to the site; (b) limited venous and lymphatic drainage caused by either obstruction or surgical resection; and (c) use of sites over joints, which increases the risk of dislodgments because of movement.

The factors associated with a poor outcome from extravasational injuries include (a) areas of the body with little subcutaneous tissue, such as the dorsum of the hand, volar surface of the wrist, and antecubital fossa, where healing is poor and vital structures are more likely to be involved; (b) concentration of extravasate; (c) increased volume and duration of contact with tissue; and (d) the type of agent.

Management

General management guidelines for an extravasation and their theoretical foundations exist (Table 52–2).

Once extravasation of an agent is suspected, the infusion should be immediately halted. A physician should be notified and the agent, its concentration, and the approximate amount infused should be noted. The venous access should be maintained so that aspiration of as much of the infusate as possible can be performed and antidote can be administered, if indicated. The amount of hyaluronidase administered at the site ranges from 150–900 units, and the working concentration of the solution depends on the area to be treated. For extravasational injuries involving a small area, the initial solution of 150 units/mL may be adequate. Otherwise, the solution may be diluted by 10-fold with normal saline to increase the amount of volume that would be needed to treat a larger surface area. If the intravenous cannula is still accessible, 1 mL

TABLE 52–2. Management of Extravasational Injuries

	Therapy	Purpose/Mechanism
General	Stop infusion and maintain intravenous cannula at the site.	
	Aspirate extravasate from the site by accessing the original intravenous cannula.	Minimizes amount of antineoplastic localized at the site.
	Irrigation of subcutaneous tissue at the site with normal saline by accessing the original intravenous cannula.	
	Apply dry cool compresses for 1 hour, every 8 hours for 3 days.	Localizes area of involvement and diminishes cellular uptake of the antineoplastic.
	Elevate extremity and administer analgesia.	Promotes drainage, prevents dependent edema, and for comfort.
Specific		
Anthracyclines	Dimethyl sulfoxide (DMSO)—55–99%. Applied topically and allowed to dry. Every 6–8 hours for 3–10 days.	Free radical scavenger.
	Dexrazoxane 1000 mg/m^2, daily, on days 1 and 2, and then 500 mg/m^2 on day 3: IV.	Limits free radical formation.
Mechlorethamine	Sodium thiosulfate—Prepare a sterile 0.17 M solution by mixing 4 mL thiosulfate 10% weight/volume with 6 mL water for injection. Infiltrate the site of extravasation.	Prevents tissue alkylation.
Mitomycin	DMSO applied topically.	Free radical scavenger.
Vinca alkaloids and epipodophyllotoxins	Hyaluronidase—Inject, intradermally or subcutaneously, 150–900 units into the site.	Degrades hyaluronic acid to enhance systemic absorption.
	Dry warm compresses.	Promotes systemic absorption.

of hyaluronidase may be administered through the catheter. Wounds that are either cancerous or infected should not be treated with hyaluronidase.

The wound should be observed closely for the first 7 days, and a surgeon consulted if either pain persists or evidence of ulceration appears.

Leucovorin (Folinic Acid) and Folic Acid

PHARMACOLOGY

Folic acid is an essential water-soluble vitamin that is the most common pharmaceutical preparation of many folate congeners. After absorption, folic acid is reduced by dihydrofolic acid reductase (DHFR) to tetrahydrofolic acid, which accepts 1-carbon groups. Tetrahydrofolic acid serves as the precursor for several biologically active forms of folic acid, including 5-formyl-tetrahydrofolic acid, which is best known as folinic acid, leucovorin, or citrovorum factor. These biologically active forms function as cofactors, providing the 1-carbon groups necessary for many intracellular metabolic reactions, including the synthesis of thymidylate and purine nucleotides, which are essential precursors of DNA.

ROLE IN METHOTREXATE TOXICITY

Methotrexate (MTX) binds to the active site of DHFR, rendering it incapable of reducing folic acid to its biologically active forms, and incapable of regenerating the necessary active forms required for the synthesis of thymidylate. At physiologic pH this binding is competitive. Because leucovorin is an active form of folate, it does not require DHFR for enzymatic interconversion and can bypass the blockade produced by MTX. Folic acid is ineffective because MTX-inactivated DHFR is unable to convert folic acid to its active forms.

ROLE IN METHANOL TOXICITY

Rats and monkeys experimentally made folate-deficient develop toxicity at lower methanol concentrations. Administration of folic acid to monkeys accelerates formate metabolism. Pretreatment with folic acid, or leucovorin, decreased formate concentrations and the accompanying metabolic acidosis, without affecting the rate of methanol elimination.

LEUCOVORIN PHARMACOKINETICS

Normal plasma folate concentrations are approximately 0.05 μmol/L. In healthy volunteers, the bioavailability of oral leucovorin decreased from 100% for a 20-mg dose to 78% for a 40-mg dose, and, ultimately, to 31% for a 200-mg dose. The 200-mg oral dose produced a peak plasma concentration of 1.82 μmol/L compared to 0.66 μmol/L for the 20-mg oral dose and 27.1 μmol/L for the 200-mg IV dose. During constant infusion the steady-state concentration for the active isomer of leucovorin is 2.33 μmol, the half-life is 35 minutes, and the volume of distribution is 13.6 L.

LEUCOVORIN DOSING FOR METHOTREXATE OVERDOSES

When a patient overdoses on MTX, a dose of leucovorin estimated to produce the same plasma concentration as the MTX dose should be given as soon as possible, preferably within 1 hour. Because of the safety of leucovorin and because of the toxicity of MTX, underdosing leucovorin should be avoided. Although plasma MTX concentrations are closely followed in on-

cology patients, in the overdose setting it is inappropriate to wait for a MTX plasma concentration before initiating treatment with leucovorin. Furthermore, in a patient not receiving MTX therapeutically, there is no need to permit any MTX to remain unantagonized by leucovorin.

For example, if a child unintentionally ingests 100 2.5-mg MTX tablets for a total dose of 250 mg, only part of this dose is absorbed because MTX absorption is saturable. In this case, it is safe to assume that a bioavailability of 50% would result in an absorbed dose of MTX of 125 mg. For this exposure, an intravenous dose of 125 mg of leucovorin could be given over 15–30 minutes. This dose of IV leucovorin should be repeated every 3–6 hours until the MTX level is less than 1×10^{-8} mol/L, and preferably zero. Because the MTX half-life may vary from 5–45 hours, leucovorin therapy should be continued for 12–24 doses (3 days), or longer if MTX concentrations are unavailable.

Unintentional overdose with intrathecal MTX is potentially quite serious and is dose dependent. In these cases, intravenous leucovorin should be administered. Intrathecal leucovorin is highly toxic and contraindicated by this route.

An intravenous leucovorin dose of 100 mg/m^2 every 6 hours should be effective in all but the most severe overdoses. A constant intravenous infusion of 21 mg/m^2/h has been safely administered for 5 days.

AVAILABILITY

Leucovorin (folinic acid) powder for injection is available in 50-, 100-, and 350-mg vials. Reconstitution with sterile water for injection—5 mL to the 50-mg vial, or 10 mL to the 100-mg vial—results in a final concentration of 10 mg/mL. Because of the calcium content, the rate of intravenous administration should not be faster than 160 mg/min in an adult. Leucovorin is also available orally in a variety of strengths, including 5-, 10-, 15-, and 25-mg tablets.

Folic acid is available parenterally in 10-mL multidose vials with 1.5% benzyl alcohol in concentrations of 5 or 10 mg/mL, from a variety of manufacturers. Once opened this vial must be kept refrigerated.

ADVERSE EFFECTS AND SAFETY ISSUES

Although reports of adverse reactions to parenteral injections of folic acid or leucovorin are uncommon, the reported adverse reactions include allergic and anaphylactoid reactions. Seizures rarely have been associated with leucovorin administration.

Leucovorin dosing for MTX overdose is described above. In contrast to MTX overdose, either folic acid or leucovorin (folinic acid) should be administered parenterally at the first suspicion of methanol poisoning. No complications are reported with the use of 50–70 mg of IV folic acid, which has been used every 4 hours for the first 24 hours to treat methanol-poisoned patients. The precise dose necessary is unknown, but 1–2 mg/kg of folic acid or leucovorin every 4–6 hours is reasonable. The folic acid or leucovorin should be continued until the methanol and formate are eliminated. As the first dose is usually administered prior to hemodialysis, a second dose should be administered at the completion of hemodialysis, because hemodialysis will probably remove this water-soluble vitamin.

53 Pharmaceutical Additives

Additives, or excipients as they are more properly termed, are necessary to act as vehicles, to add color, to improve taste, to provide consistency, to enhance stability and solubility, and to impart antimicrobial properties to medicinal formulations. Most cases of excipient toxicity involve exposure to large quantities or to prolonged or improper use (Table 53–1).

During the 20th century there were several outbreaks of toxicity associated with pharmaceutical additives in the United States (Chap. 1). The Massengill sulfanilamide disaster in 1937, the most notorious of these epidemics, involved diethylene glycol. Most recently, there was concern over potential mercury toxicity and a link to autism from the preservative thimerosal, a mercury derivative that has been used in parenteral vaccines for 70 years. No evidence has yet shown toxicity to result from routine vaccination. Although these additive-related occurrences are rare relative to the frequency of pharmaceutical additive use, they illustrate the potential of pharmaceutical additive toxicity. Unlike active ingredients, there is no specific FDA approval system for pharmaceutical excipients.

BENZALKONIUM CHLORIDE

Benzalkonium chloride (BAC) or alkyldimethyl (phenylmethyl) ammonium chloride is a quaternary ammonium cationic surfactant composed of a mixture of alkyl benzyl dimethyl ammonium chlorides. Although it is the most widely used ophthalmic preservative in the United States, it is also considered the most cytotoxic. Benzalkonium chloride is also used in otic and nasal formulations, and in some small-volume parenterals.

Ophthalmic, Nasopharyngeal, and Oropharyngeal Toxicity

The surfactant properties of BAC cause intercellular matrix dissolution of corneal epithelial cells and loss of epithelial superficial layers. Irregular and broken epithelial adenoidal cells may occur. Benzalkonium chloride may decrease the viscosity of the normal protective mucous lining of the naso- and oropharynx resulting in cytotoxicity.

BENZYL ALCOHOL

Benzyl alcohol (benzene methanol) is a colorless, oily liquid with a faint aromatic odor that is most commonly added to pharmaceuticals as a bacteriostatic agent. In 1982, a "gasping" syndrome, which includes hypotension, bradycardia, gasping respirations, hypotonia, progressive metabolic acidosis, seizures, cardiovascular collapse, and death, was first described in low-birth-weight neonates in intensive care units. All the infants had received either bacteriostatic water or sodium chloride containing 0.9% benzyl alcohol to flush intravenous catheters or in parenteral medications reconstituted with bacteriostatic water or saline. The World Health Organization (WHO) currently estimates the acceptable daily intake of benzyl alcohol to be not more than 5 mg/kg body weight.

Pharmacokinetics

In adults, benzyl alcohol is oxidized to benzoic acid, conjugated in the liver with glycine, and excreted in the urine as hippuric acid. The immature meta-

TABLE 53–1. Potential Toxicity by Organ System of Various Pharmaceutical Excipients

Cardiovascular	Ophthalmic
Chlorobutanol	Benzalkonium chloride
Propylene glycol	Chlorobutanol
Fluid and electrolyte	Renal
Polyethylene glycol	Polyethylene glycol
Propylene glycol	Propylene glycol
Sorbitol	
Gastrointestinal	
Sorbitol	
Neurologic	
Benzyl alcohol	
Chlorobutanol	
Polyethylene glycol	
Propylene glycol	
Thimerosal	

bolic capacities of infants diminish their ability to metabolize and excrete benzyl alcohol.

Neurologic Toxicity

Benzyl alcohol is believed to have a role in the increased frequency of cerebral intraventricular hemorrhages and mortality reported in very-low-birth-weight (VLBW) infants (weight <1000 g) who received flush solutions preserved with benzyl alcohol. Transient paraplegia may occur following the intrathecal or epidural administration of antineoplastics or analgesics containing benzyl alcohol as a preservative. The local anesthetic effects are most likely responsible for the immediate paraparesis, although chronic intrathecal exposure causes demyelinization.

CHLOROBUTANOL

Chlorobutanol or chlorbutol (1,1,1-trichloro-2-methyl-2-propanol) is a volatile, white crystal with an odor of camphor. Chlorobutanol is widely used as a preservative in injectable, ophthalmic, otic, and cosmetic preparations. The lethal human chlorobutanol dose is estimated to be 50–500 mg/kg.

Central Nervous System Depression

Chlorobutanol has a chemical structure similar to trichloroethanol, the active metabolite of chloral hydrate, and is believed to exhibit similar pharmacologic properties. Chlorobutanol has mild sedative and local anesthetic properties, and was formerly used therapeutically as a sedative-hypnotic.

LIPIDS

There are three types of commercial intravenous lipid drug-delivery systems available: lipid emulsion, liposomal, and lipid complex. Lipid emulsions are immiscible lipid droplets dispersed in an aqueous phase stabilized by an emul-

sifier (eg, egg or soy lecithin). Liposomes differ from emulsion lipid droplets in that they are vesicles comprised of one or more concentric phospholipid bilayers surrounding an aqueous core. Lipophilic drugs can be formulated for intravenous administration by partitioning them into the lipid phase of either an emulsion or liposome. Liposomes are capable of encapsulating hydrophilic therapeutic agents within their aqueous core to exploit lipid pharmacokinetic properties. Attaching a therapeutic agent to a lipid to form a lipid complex is another way to take advantage of lipid pharmacokinetics.

Lipids may have direct pharmacologic effects on the central nervous and immune systems. Lipid fatty acid mediators may have effects on the membrane receptor channels of *N*-methyl-D-aspartate (NMDA) receptors potentiating synaptic transmission. Dose-related CNS metabolic and neurologic effects accompanied by electroencephalographic changes consistent with encephalopathy may be observed. Immunologic dysfunction may lead to an increased susceptibility to infection, and alterations may occur in lung function and hemodynamics in patients with acute respiratory distress syndrome (ARDS). The clinical relevance of these effects remains to be assessed.

For a pharmaceutical available in more than one lipid carrier formulation (eg, amphotericin B in AmBisome, Abelcet, and Amphotec), it is important to note that any change in the lipid formulation can alter its pharmacokinetic, pharmacodynamic, and safety parameters; consequently, they are not equivalent dosage formulations. Caution should be exercised when selecting, ordering, and administering these products.

PARABENS

The parabens, or parahydroxybenzoic acids, are a group of compounds widely employed as preservatives in cosmetics, food, and pharmaceuticals. Methylparaben and propylparaben are most commonly used. The parabens have a relatively low order of toxicity; however, because of their allergenic potential, they are now considered less suitable for injectable and ophthalmic preparations.

In addition to allergic reactions, parabens have the potential to cause other adverse effects. Bilirubin displacement from albumin binding sites occurred with administration of methyl and propyl paraben. Spermicidal activity has also been demonstrated.

PHENOL

Phenol (carbolic acid, hydroxybenzene, phenylic acid, phenylic alcohol) is a colorless to light pink, caustic liquid, with a characteristic odor. Phenol is well absorbed from the gastrointestinal tract, skin, and mucous membranes, and is excreted in the urine as phenyl glucuronide and phenyl sulfate metabolites. Although there are numerous reports of phenol toxicity following intentional ingestions or unintentional dermal exposures, adverse reactions to its use as a pharmaceutical excipient are uncommon, most likely because of the small quantities used.

Consequential systemic toxicity includes CNS and respiratory depression and cardiac dysrhythmias. Systemic toxicity caused by cutaneous absorption of phenol is reported.

POLYETHYLENE GLYCOL

Polyethylene glycols (PEGs; Carbowax, Macrogol) include several compounds with molecular weights (MWs) varying from 200–40,000 daltons.

They are typically available as mixtures designated by a number denoting their average molecular weight. At room temperature, PEGs with molecular weights less than 600 daltons are clear, viscous liquids with a slight characteristic odor and bitter taste. Those PEGs with molecular weights greater than 1000 daltons are soluble solids and range in consistency from pastes and waxy flakes to powders. Commercially available products such as GoLYTELY and Colyte are solutions of PEG 3350 combined with electrolytes (PEG-ELS).

Low-molecular-weight PEG exposures have caused adverse effects similar to the chemically related toxic alcohols ethylene and diethylene glycol.

Pharmacokinetics

High-molecular-weight PEGs (>1000 daltons) are not significantly absorbed from the gastrointestinal tract; however, low-molecular-weight PEGs may be absorbed when taken orally. Once in the systemic circulation PEGs are mainly excreted unchanged in the urine, although low-molecular-weight PEGs are metabolized by alcohol dehydrogenase to hydroxyacid and diacid metabolites. PEG may also be partially broken down to ethylene glycol, although the clinical consequence of this is unknown.

Nephrotoxicity and Related Disturbances

Acute tubular necrosis with oliguria and azotemia can occur after oral and topical exposures to low-molecular-weight PEGs (200 and 300 daltons). Serum hyperosmolality and high anion gap metabolic acidosis are reported.

Neurotoxicity

There are reports of neurologic complications, such as paraplegia and transient bladder atonys, following intrathecal steroidal injections containing 3% PEG as a vehicle.

PROPYLENE GLYCOL

Propylene glycol (PG), or 1,2-propanediol, is a clear, colorless, odorless, sweet viscous liquid with antiseptic properties similar to ethanol.

Pharmacokinetics

Propylene glycol is rapidly absorbed from the gastrointestinal (GI) tract following oral administration and has a volume of distribution of approximately 0.6 L/kg. Percutaneous absorption may occur following application to damaged skin (eg, extensive burn surface areas). Most absorbed PG is hepatically metabolized sequentially by alcohol dehydrogenase and aldehyde dehydrogenase to lactic acid. Lactic acid may be additionally oxidized to pyruvic acid and then to carbon dioxide and water. The terminal half-life of PG is reported to be between 1.4 and 5.6 hours in adults, and as long as 16.9 hours in neonates.

Cardiovascular Toxicity

Preparations containing 40% PG (eg, phenytoin) are associated with hypotension, bradycardia, widening of the QRS interval, increased amplitude of T waves with occasional inversions, and transient ST elevations.

Neurotoxicity

Smaller infants appear to have a decreased ability to clear PG when compared to older children and adults. Seizures can occur, particularly in low-birth-weight infants. Propylene glycol possesses inebriating and sedating properties similar to ethanol.

Ototoxicity

The effects of PG in the human middle ear have not been studied, but toxicity in animals occurs. Nearly all medications developed for application to the external ear canal are contraindicated in patients with perforated tympanic membranes.

Fluid, Electrolyte, and Acid–Base Disturbances

Patients receiving continuous or large quantities of medications containing PG can acquire high PG concentrations, particularly those with renal or hepatic insufficiency. Propylene glycol electrolyte and metabolic disturbances are evidenced by hyperosmolality and an elevated osmolar gap attributed to the osmotically active properties of PG.

Nephrotoxicity

The chronic administration of PG may contribute to proximal tubular cell damage and subsequent decreased renal function.

SORBITOL

Sorbitol (D-glucitol) occurs naturally in the ripe berries of many fruits, trees, and plants. It is particularly useful in chewable tablets because of its pleasant taste.

Pharmacokinetics

Unlike sucrose, sorbitol is not readily fermented by oral microorganisms and is poorly absorbed from the GI tract. Any absorbed sorbitol is metabolized in the liver to fructose and glucose. Sorbitol has a caloric value of 4 kcal/g and is better tolerated by diabetics than sucrose; however, some of it is metabolized to glucose. Individuals with hereditary fructose intolerance (HFI) receiving sorbitol-containing agents are at risk of toxicity.

Gastrointestinal Toxicity

In large dosages, sorbitol can cause abdominal cramping, bloating, flatulence, vomiting, and diarrhea. Sorbitol appears to exert its cathartic effects by its osmotic properties, resulting in fluid shifts within the GI tract. Ingestion of large quantities of sorbitol (greater than 20 g/d in adults) is not recommended (Antidotes in Brief: Whole-Bowel Irrigation).

THIMEROSAL

Thimerosal (Merthiolate, Mercurothiolate), or sodium ethylmercurithiosalicylate, is an organic mercury compound that is approximately 49% elemental mercury (Hg) by weight. Thimerosal has been widely used as a preservative since the 1930s in contact lens solutions, biologics, and vaccines, particularly those in multidose containers. High-dose thimerosal exposure has resulted in

neurotoxicity and nephrotoxicity. Over the last several years, concerns have arisen about infant exposure to low-dose thimerosal through vaccinations and its effects on neurodevelopment, including possible links to causes of autism. Methylmercury is a similar, but more toxic, organic mercury compound. Maximum daily recommended methylmercury exposures range from 0.1 μg Hg/kg (US Environmental Protection Agency [EPA]) to 0.47 μg Hg/kg (WHO).

Thimerosal has been removed from most US-licensed immune globulin products. All vaccines routinely recommended for children younger than 7 years of age are either thimerosal free or contain trace amounts (<0.5 μg Hg/dose), with the exception of some inactivated influenza vaccines. Multidose vials requiring thimerosal preservative remain important for immunization programs in developing countries. When a thimerosal-containing vaccine is the only alternative, the benefits of vaccination far exceed any theoretical risk of mercury toxicity.

Pharmacokinetics

Limited pharmacokinetic data exist for thimerosal and ethylmercury. Once absorbed, thimerosal breaks down to form ethylmercury and thiosalicylate. Some ethylmercury further decomposes into inorganic mercury in the blood, and the remainder distributes into kidney and, to a lesser extent, brain tissue. Because of its longer organic chain, ethylmercury is less stable and decomposes more rapidly than methylmercury, leaving less ethylmercury available to enter the kidney and brain tissue. Ethylmercury crosses the blood–brain barrier by passive diffusion. Once intracellular, ethylmercury decomposes into inorganic mercury and bioaccumulates.

Mercurial Toxicity

Organic mercury produces several distinct CNS syndromes. There is generally no beneficial response to chelation therapy. Chapter 92 has a complete discussion of mercury.

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D. Antimicrobials

54 | Antibiotics, Antifungals, and Antivirals

The majority of the adverse effects related to antibiotics occur as a result of iatrogenic complications rather than intentional overdose. The origins of these complications are diverse and include dosing and decision errors, allergic reactions, adverse drug effects, and drug interactions.

PHARMACOLOGY AND TOXICOLOGY

Antibiotic pharmacology is aimed at the destruction of microorganisms through the inhibition of cell-cycle reproduction or by directly altering a critical function within a microorganism. Table 54–1 lists antibiotics and their associated mechanisms of antimicrobial activity. Often the mechanisms for toxicologic effects following acute overdose differ from the therapeutic mechanisms. Table 54–1 also lists the toxicologic effects and related mechanisms. Table 54–2 lists the pharmacokinetics of each class of drugs.

ANTIBACTERIALS

Aminoglycosides

As aminoglycosides are only available in parenteral and ophthalmic forms, overdoses of aminoglycoside antibiotics are almost exclusively the result of dosing errors. Fortunately, overdoses are rarely life-threatening, and most patients can be safely managed with minimal intervention. Aminoglycosides may infrequently exacerbate neuromuscular blockade by antagonism of the presynaptic calcium channel (preventing acetylcholine release), and possibly from direct blockade of postsynaptic acetylcholine receptors.

Penicillins

Acute oral overdose of penicillin-containing drugs is usually not life-threatening. The most frequent complaints following acute overdose are nausea, vomiting, and diarrhea. Rarely, hyperkalemia resulting in electrocardiographic abnormalities occurs after the rapid intravenous infusion of potassium penicillin G to patients with renal failure.

Seizures occur in humans given large intravenous or intraventricular doses of penicillins. More than 50 million units intravenously are generally required to produce seizures in adults. Penicillin-induced seizures appear to be mediated through an interaction of the drug with the picrotoxin-binding site on the neuronal chloride channel near the γ-amino butyric acid (GABA) binding site. Treatment includes GABA agonists such as benzodiazepines and barbiturates, if needed.

TABLE 54–1. Antibiotic and Antifungal Pharmacology

Drug	Pharmacology of Antibiotic Effect	Acute Overdose Adverse Effect and Related Pharmacology	Chronic Administration Adverse Effect and Related Pharmacology
Antibiotic			
Aminoglycosides	Inhibit 30s ribosomal subunit	*Neuromuscular blockade*—inhibit the release of acetylcholine from presynaptic nerve terminals and antagonist at acetylcholine receptors	*Renal toxicity/ototoxicity*—form an iron complex that inhibits mitochondrial respiration and causes lipid peroxidation
Penicillins, cephalosporins, and other β-lactams	Inhibit cell wall mucopeptide synthesis	*Seizures*—agonist at picrotoxin-binding site causing GABA antagonism	*Hypersensitivity*—immune
Chloramphenicol	Inhibits 50s ribosomal subunit and inhibits protein synthesis in rapidly dividing cells	Cardiovascular collapse	"Gray baby syndrome" Same as mechanism of action
Fluoroquinolones	Inhibit DNA topoisomerase and DNA gyrase	Same as mechanism of action; bind to cations, particularly magnesium, seizures	Not entirely known; bind to cations, particularly, magnesium; tendon rupture, hyper- and hypoglycemia
Linezolid	Inhibits bacterial protein synthesis through inhibition of *N*-formyl-methionyl-t RNA	None clinically relevant	MAOI activity: pressor response to tyramine; and serotonin syndrome with SSRI and possibly meperidine
Macrolides and ketolides	Inhibit 50s ribosomal subunit in multiplying cells	*Wide QTc*—block delayed rectifier potassium channel	Not entirely known; cytotoxic effect; exacerbation of myasthenia gravis
Sulfonamides	Inhibit *para*-aminobenzoic acid and/or *para*-amino glutamic acid in the synthesis of folic acid	None clinically relevant	Hypersensitivity—metabolite is hapten leading to *hemolysis/methemoglobinemia*—exposure to UVB causes free radical formation, which results in an oxidant stress

Tetracycline	Inhibits 30s and 50s ribosomal subunits; binds to aminoacyl transfer RNA	None clinically relevant	Unknown
Vancomycin	Inhibits glycopeptidase polymerase in cell wall synthesis	"Red-man syndrome"—anaphylactoid	Unknown
Antifungal			
Amphotericin B	Binds with ergosterol on cytoplasmic membrane to cause pores to facilitate organelle leak	Same as mechanism of action Dose-related multiorgan failure	*Nephrotoxicity*—vehicle deoxycholate may be involved; nephrocalcinosis
Triazoles and imidazoles	Increase permeability of cell membranes	None clinically relevant	None clinically relevant; ?CYP inhibition

TABLE 54–2. Antibiotic and Antifungal Pharmacokinetics

Drug	Absorption	Volume of Distribution (L/kg)	Elimination Route	Half-life (h)
Antibiotic				
Aminoglycosides	Parenteral	0.25	Renal	2–3
Penicillins, cephalosporins, and other β-lactams	Oral, parenteral	Variable	Renal (predominant)	Variable
Chloramphenicol	Oral, parenteral, otic	0.5–1.0	90% Hepatic, 10% renal	1.6–3.3
Fluoroquinolones	Oral, parenteral	Variable	Renal	3–5
Ketolides	Oral	2.9	63% Renal, 37% hepatic (50% of which is CYP3A4)	10–13
Macrolides	Oral, parenteral	Variable	Hepatic	Variable
Sulfonamides	Oral, parenteral	Variable	Hepatic	Variable
Tetracyclines	Oral	Variable	Hepatic	6–26
Vancomycin	Parenteral	0.2–1.25	Renal	4–6
Antifungal				
Amphotericin B	Parenteral	4.0	Hepatic	Unclear
Triazoles and imidazoles	Oral	Variable	Hepatic	Variable

Cephalosporins

Cephalosporins have a ring structure similar to penicillins and are generally divided into first, second, third, and fourth generations based on their antimicrobial spectrum. Effects occurring after acute overdose of cephalosporins resemble those occurring after penicillin exposure, including seizures. Management guidelines for cephalosporin overdose are similar to those of penicillin overdose.

When cephalosporins containing an *N*-methylthiotetrazole (nMTT) side chain (moxalactam, cefazolin, cefoperazone, cefmetazole, cefamandole, cefotetan) undergo metabolism, the free nMTT side chain is released. Free nMTT inhibits the enzyme aldehyde dehydrogenase and in conjunction with ethanol can cause a disulfiramlike reaction (Chap. 77). The nMTT side chain is also associated with hypoprothrombinemia, although a causal relationship is controversial.

Other β-Lactam Antibiotics

Included in this group are monobactams such as aztreonam and carbapenems such as imipenem and meropenem. Effects occurring after acute overdose of other β-lactam antibiotics resemble those occurring following penicillin exposure. Imipenem is a proconvulsant in both overdose and therapeutic dosing. Management guidelines for other β-lactam overdoses are similar to those of penicillin overdoses.

Chloramphenicol

Acute overdose of chloramphenicol commonly causes nausea and vomiting. Effects are caused by its ability to inhibit protein synthesis in rapidly proliferating cells. Metabolic acidosis occurs because of the inhibition of mitochondrial enzymes, oxidative phosphorylation, and mitochondrial biogenesis. Infrequently, sudden cardiovascular collapse may occur 5–12 hours after acute overdoses and is more frequent when serum concentrations are >50 μg/mL.

Because concentrations are not readily available, all poisoned patients should receive close observation for at least 12 hours after exposure. Orogastric lavage may be useful for recent ingestions in which the patient has not vomited, and activated charcoal 1 g/kg should be given orally. Extracorporeal means of eliminating chloramphenicol are not usually required because of its rapid metabolism. However, both hemodialysis and charcoal hemoperfusion decrease elevated plasma chloramphenicol concentrations and may be of benefit in patients with large overdoses, or in patients with severe hepatic or renal dysfunction. Exchange transfusion also lowers chloramphenicol serum concentrations in neonates. Surviving patients should be closely monitored for signs of bone marrow suppression.

The classic description of chronic chloramphenicol toxicity is the "gray baby syndrome." Children with this syndrome exhibit vomiting, anorexia, respiratory distress, abdominal distension, green stools, lethargy, cyanosis, ashen color, metabolic acidosis, hypotension, and cardiovascular collapse. The majority (90%) of a dose of chloramphenicol is metabolized via glucuronyl transferase forming a glucuronide conjugate. Infants, in particular, are predisposed to the gray baby syndrome because they have a limited capacity to conjugate chloramphenicol and concomitantly have a limited ability to excrete unconjugated chloramphenicol in the urine.

Dose-dependent bone marrow depression occurs with high serum concentrations of chloramphenicol. Clinical manifestations usually occur after several weeks of therapy and include anemia, thrombocytopenia, leukopenia, and, very rarely, aplastic anemia. Bone marrow suppression is generally reversible upon discontinuation of therapy. There is also an idiosyncratic occurrence of aplastic anemia that generally occurs in susceptible patients within 5 months of treatment.

Fluoroquinolones

The fluoroquinolones are a structurally similar, synthetically derived group of antibiotics that exhibit a diverse spectrum of antimicrobial activity. Like other antimicrobials, the fluoroquinolones rarely produce life-threatening effects following acute overdose, and most patients can be safely managed with minimal interventions. Rarely, acute overdose of a fluoroquinolone results in renal failure or seizures. Serious adverse effects related to fluoroquinolone use consist of CNS toxicity as discussed, cardiovascular toxicity, hepatotoxicity, and articular/tendon toxicity. Fluoroquinolones cause prolongation of the QTc duration that may cause torsades de pointes.

Macrolides and Ketolides

The macrolide antibiotics include various forms of erythromycin (base, estolate, ethylsuccinate, gluceptate, lactobionate, stearate), azithromycin, clarithromycin, troleandomycin, and dirithromycin. Ketolides are similar in pharmacology to macrolides; telithromycin is the only available agent at this time. Acute oral overdoses of macrolide antibiotics are usually not life-threatening and symptoms are generally confined to the gastrointestinal tract and include nausea, vomiting, and diarrhea. Erythromycin causes QTc interval prolongation and torsades de pointes. Although there are no acute overdose data regarding ketolide antibiotics, effects are expected to be similar to macrolide antibiotics.

Macrolides are inhibitors of the cytochrome P450 (CYP) 3A4 enzyme, with erythromycin being the most potent. Chapter 9 lists substrates for the CYP 3A4 system. Erythromycin also inhibits CYP 1A2. Macrolides further alter many xenobiotic concentrations by inhibiting P-glycoprotein. Telithromycin exacerbates neuromuscular symptoms in patients with myasthenia gravis and can produce bronchospasm.

Sulfonamides

Acute oral overdoses of sulfonamides are usually not life-threatening and symptoms are generally confined to nausea, although allergy, methemoglobinemia, and hemolysis occur rarely. Treatment is similar to acute oral penicillin overdoses.

Tetracyclines

Significant toxicity after acute overdose of tetracyclines is unlikely. Gastrointestinal effects consisting of nausea, vomiting, and epigastric pain have been reported. Outdated older formulations of tetracycline were reported to cause hypouricemia, hypokalemia, and a proximal and distal renal tubular acidosis. This is no longer a concern when current formulations become outdated.

Vancomycin

Acute oral overdoses of vancomycin rarely cause significant toxicity and most cases can be treated with supportive care alone. Multiple-dose activated charcoal

therapy decreases the half-life of vancomycin and can be considered in patients with large overdoses when the patient is expected to have a long clearance time. Patients who receive intravenous vancomycin may develop the "red man syndrome" through an anaphylactoid mechanism. Symptoms include chest pain, dyspnea, pruritus, urticaria, flushing, and angioedema. Signs and symptoms spontaneously resolve, typically within 15 minutes. Other symptoms attributable to red man syndrome may include hypotension, cardiovascular collapse, and seizures. The incidence of red man syndrome appears to be related to the rate of infusion.

ANTIFUNGALS

Numerous antifungals are available. Toxicity related to the use of antifungal agents is variable and is generally based on their mechanism of action.

Amphotericin B

There are several case reports of amphotericin B overdose in infants and children. Significant clinical findings include hypokalemia, aspartate aminotransferase elevations, multiorgan failure, and cardiac complications, including dysrhythmias and cardiac arrest after being given 5–15 mg/kg of amphotericin B. Development of lipid and colloidal formulations of amphotericin B attenuate the adverse effects associated with amphotericin B. Care should be employed when dosing of amphotericin B as these are not interchangeable and errors in dosing have resulted in fatalities.

Infusion of amphotericin B results in fever, rigors, headache, nausea, vomiting, hypotension, tachycardia, and dyspnea. Eighty percent of patients exposed to amphotericin B will sustain some degree of renal insufficiency. Distal renal tubule damage causes potassium and magnesium wasting, proteinuria, decreased renal concentrating ability, renal tubular acidosis, and hematuria.

Azole Antifungals: Triazole and Imidazoles

Severe toxicity is not expected in the overdose setting. Hepatotoxicity, thrombocytopenia, and neutropenia are rare. The majority of toxic effects noted after the use of these drugs result from their drug interactions. Fluconazole, itraconazole, ketoconazole, and miconazole competitively inhibit CYP 3A4, the enzyme system responsible for the metabolism of many drugs.

ANTIBIOTICS SPECIFIC TO THE TREATMENT OF HUMAN IMMUNE DEFICIENCY VIRUS AND RELATED INFECTIONS

The evaluation and management of patients infected with the human immunodeficiency virus (HIV) and associated acquired immune deficiency syndrome (AIDS) are ever evolving at a rapid and progressive pace. Medications used to manage these disorders have increased the life expectancy of these patients dramatically as new, more powerful antiviral agents and drug combinations are available. Drug therapy for HIV commonly consists of a combination of agents from different classes. Table 54–3 lists the common agents used to treat HIV-related opportunistic infections; Table 54–4 lists common adverse drug effects and overdose effects, if known, for these agents.

Specific Antiretroviral Classes

Nucleoside Analog Reverse Transcriptase Inhibitors

The nucleoside analog reverse transcriptase inhibitors (NRTIs) inhibit the reverse transcription of viral RNA into proviral DNA. Currently available agents include

TABLE 54–3. Antimicrobials Used to Treat Opportunistic Infections

Drugs	Opportunistic Infection
Albendazole	Microsporidiosis
Amphotericin B	Aspergillosis
	Coccidioidomycosis
	Cryptococcus
	Histoplasmosis
	Leishmaniasis
	Paracoccidioidomycosis
	Penicilliosis
Antimony (pentavalent)	Leishmaniasis
Atovaquone	*Pneumocystis jiroveci* pneumonia
Azithromycin	*Mycobacterium avium* complex
Clarithromycin	
Caspofungin	Aspergillosis
Clindamycin	*Pneumocystis jiroveci* pneumonia
	Toxoplasma gondii encephalitis
Dapsone	*Pneumocystis jiroveci* pneumonia
Ethambutol	*Mycobacterium avium* complex
Fluconazole	Coccidioidomycosis
	Histoplasmosis
Flucytosine	Cryptococcus
Foscarnet	Cytomegalovirus
Fumagillin	Microsporidiosis
Ganciclovir	Cytomegalovirus
Itraconazole	Histoplasmosis
Leucovorin	*Pneumocystis jiroveci* pneumonia
	Toxoplasma gondii encephalitis
Nitazoxanide	Cryptosporidiosis
	Microsporidiosis
Paromomycin	Cryptosporidiosis
Pentamidine	*Pneumocystis jiroveci* pneumonia
Primaquine	*Pneumocystis jiroveci* pneumonia
Pyrimethamine	*Toxoplasma gondii* encephalitis
Rifabutin	*Mycobacterium avium* complex
Sulfadiazine	*Toxoplasma gondii* encephalitis
TMX-SMX	*Pneumocystis jiroveci* pneumonia
	Toxoplasma gondii encephalitis
	Isosporiasis
Trimetrexate	*Pneumocystis jiroveci* pneumonia
Valganciclovir	Cytomegalovirus
Voriconazole	Aspergillosis

TMX-SMX = trimethoprim and sulfamethoxazole.

abacavir (ABC), adefovir (PMEA), emtricitabine (FTC), didanosine (ddI), lamivudine (3TC), stavudine (d4T), zidovudine (AZT, ZDV), and zalcitabine (ddC). Many intentional overdoses of reverse transcriptase inhibitors occur without major toxicologic effect. The most serious adverse effect anticipated after acute overdose of an NRTI is the development of a lactic acidosis, which appears to be more common in women. This occurs after incorporation of the nucleoside analog into mitochondrial DNA by RNA polymerase, causing inhibition of DNA polymerase, which results in decreased production of mitochondrial DNA electron transport proteins, and, ultimately, inhibits oxidative phosphorylation. Other common

TABLE 54–4. Antimicrobials Used in the Treatment of HIV-Related Infections

Drugs	Common Overdose Effects	Common Adverse Drug Effects
Albendazole	No reported cases	Increased AST/ALT, nausea, vomiting, and diarrhea. Hematologic toxicity; rare—encephalopathy, renal failure, rash
Antimony (pentavalent)	Acute tubular necrosis	Acute tubular necrosis. Multiorgan system failure
Atovaquone	No clinical relevant effects	Rashes, anemia, leukopenia, increased AST/ALT
Caspofungin	No reported cases	Phlebitis, headache, hypokalemia, increased AST/ALT, fever
Flucytosine	No reported cases	Bone marrow suppression, hepatotoxicity, nausea, vomiting, diarrhea, and rash
Foscarnet	No reported cases	Azotemia, hypocalcemia, and renal failure are most consequential; may also result in anemia, leukopenia, thrombocytopenia, fever, headache, seizures, genital and oral ulcers, fixed-drug eruptions, nausea, vomiting, diarrhea, headaches, seizures, coma, diabetes insipidus, hypophosphatemia, hypokalemia, and hypomagnesemia
Fumagillin	No reported cases	Neutropenia and thrombocytopenia
Ganciclovir	No clinical relevant effects	Leukopenia, worsening of renal function; can also cause nausea, vomiting, diarrhea, increased AST/ALT, anemia, thrombocytopenia, headache, dizziness, confusion, seizures
Nitazoxanide	No reported cases	Hypotension, headache, abdominal pain, nausea, vomiting; may cause green-yellow urine discoloration
Pentamidine	40 times dosing error in a 17-month-old child resulted in cardiac arrest	Hypoglycemia (early) followed by hyperglycemia, azotemia; can cause hypotension, torsades de pointes, phlebitis, rash, Stevens-Johnson syndrome, hypocalcemia, hypokalemia, anorexia, nausea, vomiting, metallic taste, leukopenia, and thrombocytopenia
Primaquine	No reported cases	Granulocytopenia, hemolytic anemia, methemoglobinemia, leukocytosis; potential for hypertension
Pyrimethamine	No reported cases	Agranulocytosis, aplastic anemia, thrombocytopenia, and leukopenia
Rifabutin	High doses (>1 g daily): arthralgia/arthritis	Nausea, vomiting, diarrhea; can cause hepatotoxicity, neutropenia, thrombocytopenia, and hypersensitivity reactions
Sulfadiazine	Acute renal failure and hypoglycemia	Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme; can cause headaches, depression, hallucinations, ataxia, tremor, crystalluria, hematuria, proteinuria, and nephrolithiasis
Trimetrexate	No reported cases; treat similar to methotrexate (Chap. 52)	Myelosuppression, nausea, vomiting, histamine reactions
Valganciclovir	No reported cases; expect to be similar to ganciclovir	Anemia, neutropenia, thrombocytopenia; nausea, vomiting, headache, and peripheral neuropathy

adverse effects are somewhat agent specific and include hematologic toxicity after zidovudine, pancreatitis with didanosine, hypersensitivity after abacavir, and sensory peripheral neuropathy after zalcitabine, stavudine, and didanosine.

Nonnucleoside Reverse Transcriptase Inhibitors

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) bind directly to reverse transcriptase enzyme, enabling allosteric inhibition of enzymatic function. Delavirdine, nevirapine, and efavirenz are the currently available agents. There are currently no substantial acute overdose data on these drugs, although they generally appear to be safe in overdose.

Protease Inhibitors

Protease inhibitors inhibit the vital enzyme (proteinase), which is required for viral replication. Currently available agents include amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir mesylate. Overdose data are limited. A review of data submitted to the manufacturer of indinavir found that of 79 reports, the sole complaints included nausea, vomiting, abdominal pain, and nephrolithiasis.

55 Antituberculous Medications

HISTORY AND EPIDEMIOLOGY

The global burden of tuberculosis is enormous. Approximately 2 billion people are infected with *Mycobacterium tuberculosis*; 7.96 million new cases are diagnosed each year. Concurrently, multidrug-resistant tuberculosis emerged as a serious health concern and has forced the use of multidrug regimens, as well as the reintroduction of older antituberculous agents. This approach increases the incidence of adverse drug effects. Moreover, many patients receiving antituberculous therapy are chronically ill and have an increased risk of suicidality and, potentially, intentional overdose.

ISONIAZID

Pharmacology

Isoniazid (INH) interacts with InhA, a mycobacterial enzyme that is required for the synthesis of very-long-chain lipids (mycolic acids) that are important components of mycobacterial cell walls. Isoniazid itself does not directly interact with the InhA enzyme. Instead, INH is a prodrug that undergoes metabolic activation by a mycobacterial catalase-reductase known as KatG to produce a highly reactive intermediate. This INH-derived species enters the binding site of InhA where it is covalently linked to the reduced form of nicotinamide adenine dinucleotide (NADH), irreversibly inhibiting this enzyme.

Pharmacokinetics and Toxicokinetics

INH is rapidly absorbed, reaching peak plasma concentrations within 2 hours, diffuses into all body fluids with a volume of distribution of approximately 0.6 L/kg, and has negligible binding to serum proteins. The primary metabolic pathway for INH is via *N*-acetylation by the enzyme *N*-acetyltransferase. Patients with the polymorphic forms of *N*-acetyltransferase are distinguishable phenotypically as slow and fast acetylators. The slow acetylation isoform is found in 50–60% of American whites and African Americans, whereas the fast acetylator isozymes are found in 90% of Asians and Inuits. The elimination half-life of INH is approximately 70 minutes in fast acetylators, and 180 minutes in slow acetylators. Isoniazid is transformed either via a stepwise process to acetylhydrazine and isonicotinic acid, or directly to hydrazine (Figure 55–1).

Mechanism of Toxicity

Isoniazid creates a functional deficiency of pyridoxine by at least two mechanisms. Hydrazone INH metabolites inhibit pyridoxine phosphokinase, the enzyme that converts pyridoxine to its active form, pyridoxal-5-phosphate. In addition, INH reacts with pyridoxal phosphate to produce an inactive hydrazone complex that is renally excreted. This interferes with the synthesis and metabolism of γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the CNS. Depletion of GABA is thought to be the etiology of

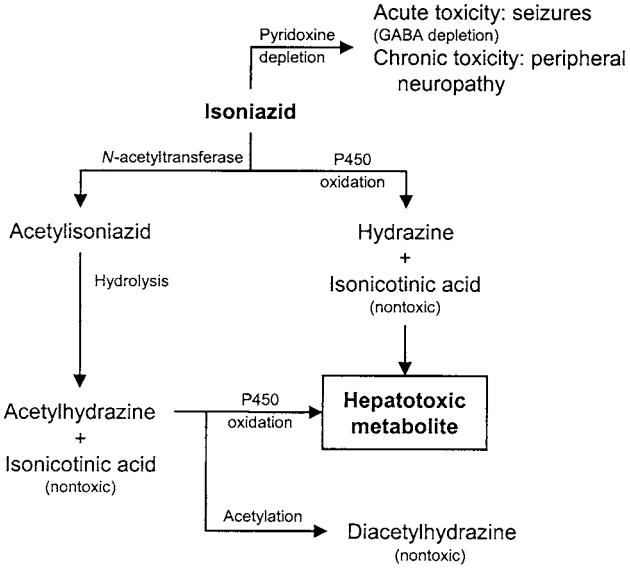


FIG. 55–1. Metabolism of INH. Acetylator status is determined by polymorphism in *N*-acetyltransferase.

INH-induced seizures. Structurally similar hydrazines exert similar acute toxic effects (Chap. 113).

Clinical Manifestations of INH Toxicity

Acute Toxicity

Isoniazid produces the triad of seizures refractory to conventional therapy, severe metabolic acidosis, and coma. These clinical manifestations may appear as soon as 30 minutes following ingestion. Although vomiting, slurred speech, dizziness, and tachycardia may represent early manifestations of toxicity, seizures may be the initial sign of acute overdose. Seizures may occur following the ingestion of greater than 20 mg/kg of INH, and invariably occur with ingestions greater than 35–40 mg/kg. Protracted coma typically occurs with acute severe INH toxicity. Coma may last as long as 24–36 hours and persist beyond the termination of seizure activity, as well as the resolution of acidemia. Additional sequelae from acute INH toxicity include hypotension, hyperpyrexia, renal failure, hyperglycemia, glycosuria, and ketonuria.

Chronic Toxicity

Chronic therapeutic INH use is associated with a variety of adverse effects. The most disconcerting is hepatocellular necrosis. Although asymptomatic elevation of aminotransferases is common in the first several months of treatment, laboratory testing may reveal the onset of hepatitis up to 1 year after starting INH therapy. Clinically relevant hepatitis occurs in only 0.1% of patients appropriately selected for therapy. The death rate from INH hepatotoxicity is only 0.001%.

Peripheral neuropathy and optic neuritis are known adverse drug effects of chronic INH use. Neurotoxicity is probably caused by pyridoxine deficiency aggravated by the formation of pyridoxine-INH hydrazones, and most commonly presents in a stocking-glove distribution that progresses proximally. Although primarily sensory in nature, myalgia and weakness may occur. Optic neuritis presents as decreased visual acuity; visual field testing may reveal central scotomata. Isoniazid is also associated with CNS toxicity, with findings of ataxia, psychosis, hallucinosis, and coma.

Diagnostic Testing

Acute INH toxicity is a clinical diagnosis that may be inferred by history and confirmed by measuring serum INH concentrations. Acute toxicity from INH has been defined as a serum INH concentration greater than 10 mg/L at 1 hour after ingestion, greater than 3.2 mg/L at 2 hours after ingestion, or greater than 0.2 mg/L at 6 hours after ingestion. Because serum INH concentration measurements are not widely available, clinicians cannot rely on serum concentrations to confirm the diagnosis or initiate therapy. Because of the risk of hepatitis associated with chronic INH use, hepatic aminotransferases should be regularly monitored once therapy is started.

Management

Acute Toxicity

The initial management requires termination of seizure activity, fluid resuscitation, and stabilization and correction of vital signs with maintenance of a patent airway. Clinicians should consider the administration of sodium bicarbonate to treat severe acidemia with a pH <7.0. Gastrointestinal decontamination should be performed with activated charcoal when there are no contraindications (Chap. 8). The antidote for INH-induced neurologic dysfunction is pyridoxine. Pyridoxine rapidly terminates seizures, corrects metabolic acidosis, and reverses coma. To treat acute toxicity, the intravenous pyridoxine dose in grams should equal the amount of INH ingested in grams with a first dose in an adult of up to 5 g. Unknown quantities of ingested INH warrant initial empiric treatment with a pyridoxine dose of no more than 5 g (pediatric dose: 70 mg/kg to a maximum of 5 g). Benzodiazepines should always be used for their synergistic effects with pyridoxine.

Asymptomatic patients who present to the emergency department within 2 hours of ingestion of toxic amounts of INH should receive prophylactic administration of 5 g pyridoxine. Asymptomatic patients may be observed for a 6-hour period for signs of toxicity. Acute toxicity is unlikely to first appear more than 6 hours beyond ingestion.

Although hemodialysis has been used to enhance elimination of INH in acute overdose, with clearance rates reported as high as 120 mL/min, hemodialysis is rarely indicated.

Chronic Toxicity

Hepatitis (defined as aminotransferase concentrations 2–3 times baseline levels) resulting from therapeutic INH administration mandates termination of therapy. Pyridoxine does not reverse hepatic injury; consequently, surveillance for and recognition of hepatocellular injury remains essential. Peripheral Neuropathy is commonly prevented or treated with as much as 50 mg/d of oral pyridoxine, although lower doses may be effective.

RIFAMYCINS

Pharmacology

Rifamycins are a class of semisynthetic macrocyclic antibiotics derived from *Streptomyces mediterranei*. Drugs in this class include rifampin, rifabutin, and rifapentine, of which the first two are most commonly used. Rifampin inhibits the initial steps in RNA chain polymerization through the formation of a stable complex with RNA polymerase. Disruption of RNA synthesis interrupts protein synthesis, leading to cell death.

Pharmacokinetics and Toxicokinetics

Oral rifampin reaches peak plasma concentrations in 2–4 hours. Rifampin is secreted into the bile and undergoes enterohepatic recirculation. The half-life of rifampin, which is normally 1.5–5 hours, increases with hepatic dysfunction. However, rifampin induces its own metabolism to shorten its half-life by approximately 40%. Rifampin is approximately 75% protein-bound and distributes widely into body compartments.

Clinical Manifestations

Acute Toxicity

Isolated rifamycin overdose infrequently produces serious acute effects. The most common side effects of acute rifampin overdose are GI symptoms consisting of epigastric pain, nausea, vomiting, and diarrhea. The presence of diarrhea distinguishes rifampin ingestion from overdose of other antimycobacterial agents. Nonetheless, three deaths are associated with rifampin or rifampicin ingestion; an autopsy performed following one of these deaths identified pulmonary edema. Other effects include flushing, angioedema, and obtundation; children who receive an overdose of rifampin may develop facial or periorbital edema. Anterior uveitis is occasionally observed, as are neurologic effects consisting of generalized numbness, extremity pain, ataxia, and muscular weakness.

Chronic Toxicity

Hepatitis occurs more frequently in patients taking combination therapy of rifampin and INH than in those taking INH alone. This may result from rifampin's ability to induce cytochromes responsible for INH hepatotoxicity. Liver injury, when attributable to rifampin alone, is predominantly cholestatic, prompting suggestions that clinical surveillance for hepatic injury may be preferable over regular biochemical monitoring.

Management

Management of patients with acute rifampin overdose is primarily supportive. Stabilization of vital signs and administration of activated charcoal are usually adequate, although clinicians should remain vigilant for coingestants.

ETHAMBUTOL

Pharmacology and Pharmacokinetics

Ethambutol, an antibiotic to which almost all strains of *M. tuberculosis* are sensitive, has no effect on other bacteria. Ethambutol binds to arabinosyl-

transferases, which are enzymes that incorporate glycan subunits into cell wall polymers known as arabinogalactan and lipoarabinomannan.

Maximum serum concentrations are reached within 4 hours of oral administration. Ethambutol is approximately 20–30% protein bound and has a half-life of 4–6 hours. Three-fourths of a standard dose is excreted unchanged into the urine by a combination of glomerular filtration and tubular secretion.

Clinical Manifestations and Management

Acute overdosage of ethambutol is generally well tolerated, although death is reported. More commonly, nausea, abdominal pain, confusion, visual hallucinations, and optic neuropathy occur following acute ingestions of greater than 10 g. Although stabilization of vital signs and GI decontamination consisting of activated charcoal remain the hallmarks of therapy, clinicians must remain vigilant for coingestants, particularly INH.

The most significant adverse effect of the therapeutic use of ethambutol is dose-related optic or retrobulbar neuritis, which may be unilateral or bilateral. Approximately 15% of patients receiving 50 mg/kg/d, 5% of patients receiving 25 mg/kg/d, and fewer than 1% of those receiving 15 mg/kg/d develop optic neuritis. Patients may complain of decreased visual acuity, loss of red/green discrimination, and loss of peripheral vision. Management of chronic toxicity from ethambutol involves cessation of therapy, although improvement may be hastened by treatment with hydroxocobalamin.

Diagnostic Testing

All patients should receive neuro-ophthalmic testing prior to ethambutol therapy. The use of visual evoked potentials is especially useful in identifying subclinical optic nerve disease. Furthermore, patients should receive regular visual acuity examinations, and clinicians should encourage patients to report any subjective symptoms related to vision.

PYRAZINAMIDE

Pharmacology and Pharmacokinetics

Pyrazinamide (PZA) is a structural analog of nicotinamide whose mechanism of action is similar to that of INH. Like INH, PZA is a prodrug. The precise cellular functions inhibited by pyrazinoic acid have not been defined. After oral administration, PZA is rapidly absorbed, with maximum concentrations occurring within 1 hour of administration. The volume of distribution of PZA is 0.7 L/kg, and approximately 10% remains bound to plasma protein. Pyrazinamide is metabolized to pyrazinoic acid and 5-hydroxypyrazinoic acid, which are then renally excreted. The drug has a half-life of approximately 9 hours.

Clinical Manifestations and Management

Proper dosing of PZA and short courses of therapy are the most important factors in preventing hepatotoxicity. Treatment for hepatotoxicity involves cessation of PZA therapy in conjunction with supportive care. Pyrazinamide also inhibits the renal excretion of uric acid, and hyperuricemia is observed. While most patients regardless of age remain asymptomatic and do not develop symptoms of gout, polyarthralgias responsive to probenecid or allopur-

inol may be observed. Toxic effects from acute overdose of pyrazinamide have not been reported.

CYCLOSERINE

Cycloserine is used in conjunction with other tuberculostatic agents when treatment with primary agents (INH, rifampin, PZA, ethambutol, and streptomycin) has failed. Cycloserine, a structural analog of alanine, inhibits reactions in which D-alanine is required for cell wall biosynthesis. After oral doses, 70–90% of the drug is absorbed. Peak concentrations of the drug are reached in 3–4 hours. Cycloserine is distributed throughout all tissues and body fluids and easily crosses the blood–brain barrier. Very little of the antibiotic is metabolized, and the drug is excreted unchanged in the urine.

Toxicity, occurring in as many as 50% of patients taking cycloserine, is dose dependent. Neurologic effects consist of somnolence, headache, tremor, dysarthria, vertigo, confusion, irritability, and seizures. Psychiatric manifestations include paranoid reactions, depression, and suicidal ideation. Toxicity is potentiated by alcohol, usually appears within the first 2 weeks of therapy, and ceases upon termination of the drug. Because cycloserine is renally excreted, patients with renal failure may be predisposed to toxicity; it is removed by hemodialysis. Reports of overdose are lacking in the English medical literature.

OTHER ANTIMYCOBACTERIAL AGENTS

Ethionamide, a congener of INH, is thought to have a mechanism of action similar to that of INH. Oral doses yield peak serum concentrations within approximately 3 hours of administration. The half-life of the drug is approximately 2 hours. Toxic effects include orthostatic hypotension, depression, and drowsiness. Rash, purpura, and gynecomastia are observed, as are tremor, paresthesia, and olfactory disturbances. Approximately 5% of patients receiving ethionamide develop hepatitis. Treatment for toxicity involves withholding ethionamide therapy. There are no reports of toxicity from ethionamide overdose in the English literature.

Para-aminosalicylic acid (PAS) is thought to inhibit enzymes responsible for folate biosynthesis in mycobacteria, but not in other organisms. PAS is readily absorbed from the gut and is rapidly distributed into all tissues, especially the pleural fluid and caseous material. Para-aminosalicylic acid has a half-life of minutes and is renally excreted. Adverse effects associated with PAS use include nausea, vomiting, diarrhea, sore throat, and malaise. Between 5 and 10% of patients receiving PAS develop hypersensitivity reactions characterized by high fever, rash, and arthralgias. Para-aminosalicylic acid may be removed by hemodialysis in patients with renal failure.

Capreomycin is a cyclic polypeptide with an unknown mechanism of action. Because of poor absorption after oral dosing, capreomycin must be administered intramuscularly. Toxicity associated with capreomycin use includes hearing loss, tinnitus, proteinuria, and electrolyte disturbances, although severe renal failure is rare. Eosinophilia, leukocytosis, and rashes have been described.

Pyridoxine

Pyridoxine (vitamin B_6), a water-soluble vitamin, is administered as an antidote for isonicotinic acid hydrazide (isoniazid, INH), hydrazine, and methylated hydrazines, and ethylene glycol overdoses.

CHEMISTRY

Pyridoxine hydrochloride was chosen as the commercial preparation because of its stability. The active form of pyridoxine is the phosphate ester of pyridoxal (pyridoxal-5′-phosphate [PLP]).

PHARMACOLOGY

PLP is an important cofactor in more than 100 enzymatic reactions, including decarboxylation and transamination of amino acids, and the metabolism of tryptophan to 5-hydroxytryptamine and methionine to cysteine. Iatrogenic pyridoxine deficiency in animals produces seizures associated with reduced brain concentrations of PLP, glutamic acid decarboxylase, and γ-aminobutyric acid (GABA).

PHARMACOKINETICS

Pyridoxine is not protein bound, has a volume of distribution of 0.6 L/kg, and easily crosses cell membranes; in contrast, PLP is nearly entirely plasma protein bound. After intravenous infusion of 100 mg of pyridoxine over 6 hours, PLP concentration increases rapidly in plasma and in erythrocytes. Oral pyridoxine in doses of 600 mg is 50% absorbed within 20 minutes of ingestion by a first-order process with rapid achievement of peak plasma concentrations of pyridoxine, PLP, and pyridoxal.

MECHANISM OF HYDRAZIDE AND HYDRAZINE-INDUCED SEIZURES

The antidotal role of pyridoxine in the management of poisoning from INH and methylated hydrazines like monomethylhydrazine (MMH) is based on the interference of these xenobiotics on the normal use and function of pyridoxine. Specifically, INH and other hydrazides and hydrazines inhibit the enzyme pyridoxine phosphokinase, which converts pyridoxine to PLP. In addition, hydrazides directly combine with PLP, causing inactivation through the production of hydrazones, which are rapidly excreted by the kidney. PLP is a coenzyme for L-glutamic acid decarboxylase, which permits the synthesis of GABA from L-glutamic acid. The decreased GABA formation reduces cerebral inhibition, which may contribute in part to the development of seizures.

In a dog model of INH-induced toxicity, pyridoxine reduced the severity of seizures, the time to seizure, and prevented the mortality of a previously lethal dose of INH in a dose-dependent fashion. As single agents, phenobarbital, pentobarbital, phenytoin, ethanol, and diazepam were ineffective in controlling seizures and mortality, but when combined with pyridoxine, each protected the animals from seizures and death.

Clinical experience with INH overdose in humans demonstrates rapid seizure control following pyridoxine administration. In addition to controlling seizures, the administration of pyridoxine also appears to restore consciousness. Similar experiences are reported for MMH poisoning and ingestion of the false morel mushroom *Gyromitra esculenta*.

ETHYLENE GLYCOL

PLP is a cofactor in the conversion of glycolic acid to nonoxalate compounds. Patients poisoned with ethylene glycol should receive pyridoxine IV in an attempt to shunt metabolism preferentially away from the production of oxalic acid.

SAFETY ISSUES

Pyridoxine is neurotoxic to animals and humans when administered chronically in supraphysiologic doses. Delayed peripheral neurotoxicity occurred in patients taking daily doses of 200 mg to 6 g of pyridoxine for 1 month. Healthy volunteers administered 1 or 3 g/d developed a distal sensory axonopathy after 1.5 months in the high-dose and 4.5 months in the low-dose regimens. Pyridoxine may also induce a sensory neuropathy when massive doses are administered either as a single dose or over several days. Acute dosing in excess of 375 mg/kg carries a similar risk potential.

DOSING

A safe and effective pyridoxine regimen for INH overdoses in adults is 1 g of pyridoxine for each gram of INH ingested, to a maximum of 5 g or 70 mg/kg. Initial doses of pyridoxine in children probably should not exceed 70 mg/kg. These doses are sufficient in the majority of patients but can be repeated if necessary. For active seizures, pyridoxine may be given by slow IV infusion at approximately 0.5 g/min until the seizures stop or the maximum dose has been reached. When the seizures stop, the remainder of the dose should be infused over 4–6 hours to maintain pyridoxine availability while the INH is being eliminated. In the event of inadequate availability of intravenous pyridoxine, pyridoxine should be administered orally.

Using the INH dosage regimen is theoretically reasonable for MMH and *Gyromitra* spp but has never been tested in humans. Pyridoxine should not be the sole agent used for INH or MMH poisoning. A benzodiazepine should be used with pyridoxine in an attempt to achieve synergistic control of seizures. If the seizures do not respond to the initial therapeutic interventions, they can be repeated, followed by intravenous agents such as propofol, pentobarbital, or phenobarbital, and, if necessary, neuromuscular blockade and general anesthesia.

AVAILABILITY

Pyridoxine HCl is available parenterally at a concentration of 100 mg/mL in 1-mL ampules from various manufacturers. An IV dose of 5 g of pyridoxine requires 50 (1-mL) ampules containing 100 mg/mL. This is an exception to the rule that appropriate doses of medications rarely require multiple dosages of this magnitude. This also emphasizes the necessity of keeping an adequate supply available in the emergency department as well as in the pharmacy. Oral pyridoxine is available in many tablet strengths from 10–500 mg from various manufacturers.

56 Antimalarials

The malaria parasite has caused untold grief throughout human history. Today, 40% of humanity lives in areas of endemic malaria. One-half billion people suffer infection and 2 million die each year. Included in those at risk are 50 million travelers from industrialized countries who visit the developing world each year. In spite of prophylactic medications, 30,000 of these travelers will acquire malaria. Tables 56–1 and 56–2 list normal dosing regimens and pharmacokinetics of the antimalarials.

QUININE

In addition to its use as an antimalarial, quinine has been used for muscle cramps and, because of its extremely bitter taste (similar to heroin), as an adulterant in drugs of abuse.

Pathophysiology

Quinine inhibits cardiac sodium and potassium channels. Sodium channel blockade produces negative inotropy, slows the rate of depolarization, slows conduction, and increases action potential duration. This inhibition of the inward sodium current is increased at higher heart rates. Inhibition of the potassium channels results in suppression of the repolarizing delayed rectifier potassium current, particularly the rapidly activating component. The resultant increase in the effective refractory period is also rate dependent, but with greater repolarization delay occurring at slower heart rates.

The mechanism of quinine-induced inhibition of hearing is multifactorial. Microstructural changes of the outer hair cells of the cochlea and organ of Corti are noted histologically. Vasoconstriction and local prostaglandin inhibition within the organ of Corti may contribute to the inhibition of hearing. Inhibition of the potassium channel may also be responsible for hearing loss and vertigo.

The ophthalmic toxicity of quinine is most likely a direct retinal toxic effect. Electroretinographic studies demonstrate a rapid and direct effect on the retina (decreased potentials) within minutes after quinine dosing. These early retinographic changes, as well as histologic lesions in photoreceptor and ganglion cell layers, provide evidence of direct damage. Changes in the electrooculogram, suggesting changes in the retinal pigment epithelium, parallel changes in visual acuity.

Quinine also inhibits the adenosine triphosphate (ATP)-sensitive potassium channels of the pancreatic β cells, resulting in the release of insulin similar to the action of sulfonylureas. Although mild hyperinsulinemia may occur, hypoglycemia is unusual following oral quinine overdose.

Clinical Manifestations

With therapeutic doses, patients often experience "cinchonism." Common features include nausea, vomiting, decreased hearing acuity, tinnitus, and headache. Tachycardia is often noted. Diarrhea and abdominal pain are less frequently observed. The skin may be warm and flushed. As plasma concen-

TABLE 56–1. Common Adult Doses of Antimalarials Used Worldwide

Drug	Prophylactic Dose (Adult)	Upper Dose Range, Treatment (Adult)[a]
Quinine sulfate	Not used	650 mg tid × 7 days[b]
Chloroquine phosphate	500 mg/wk as single dose	1000 mg STAT, then 500 mg at 6 h, 24 h, and 48 h
Hydroxychloroquine sulfate	400 mg/wk as single dose	Rarely used
Primaquine phosphate	30 mg of base/d × 14 days[c]	30 mg of base/d × 14 days
Halofantrine	Not used	500 mg q6h × 3 doses, repeat in 7 days
Amodiaquine	Not used	10 mg of base/kg/d × 3 days
Mefloquine	250 mg/wk as single dose	750 mg STAT, then 500 mg 8 h later
Pyrimethamine-sulfadoxine	Not used	75 mg pyrimethamine + 1500 mg sulfadoxine as single dose
Artemisinin	Not used	10 mg/kg × 7 days
Artesunate	Not used	2 mg/kg PO BID on day 1, then 2 mg/kg/d × 6[d] or 2.4 mg/kg IV on day 1 then 1.2 mg/kg/d IV or PO × 6 days
Artemether	Not used	3.2 mg/kg IM on day 1 then 1.6 mg/kg/d IM or PO × 6 days
Artemether-lumefantrine	Not used	80 mg artemether + 480 mg lumefantrine at 0, 8, 24, 36, 48, and 60 h
Doxycycline	100 mg/d	100 mg BID[e]
Proguanil-atovaquone	100 mg proguanil + 250 mg atovaquone once per day	400 mg proguanil + 1000 mg atovaquone per day × 3 days
Proguanil-chloroquine	200 mg proguanil + 100 mg chloroquine once per day	Not used

[a]Choice, duration, and dosage may vary with malarial species and frequency of drug resistance in the geographic area.
[b]Usually with doxycycline, tetracycline, or clindamycin for chloroquine-resistant cases.
[c]After leaving *Plasmodium vivax* or *Plasmodium ovale* area.
[d]Often with mefloquine 15 mg/kg in a shorter course.
[e]With quinine sulfate for chloroquine-resistant cases.

trations rise, visual disturbances, including blindness, are common. Patients experience vertigo, dystonia, syncope, ventricular dysrhythmias (including torsades de pointes), and hypoglycemia. The average lethal oral dose of quinine is 8 g, although a dose as small as 1.5 g has been reported to cause death. Delirium, coma, and seizures usually occur only after severe overdoses and may be associated with myocardial depression.

Cardiovascular manifestations include prolongation of the PR interval, QRS complex, and QTc, as well as ST depression with or without T-wave inversion. Patients may develop complete heart block, markedly prolonged QRS complexes, or dysrhythmias. Quinine toxicity can also result in significant hypotension because of vasodilation and probably a concomitant decrease in myocardial contractility.

Ophthalmic presentations include blurred vision, visual field constriction, tunnel vision, diplopia, altered color perception, mydriasis, photophobia,

TABLE 56–2. Pharmacokinetic Properties of Antimalarials

	Quinine	Chloroquine	Primaquine	Mefloquine	Halofantrine	Pyrimethamine	Dapsone
Bioavailability (%)	76	80	74	>85	Low, varies	>95	90
Time to peak (oral)	1–3 h	2–5 h	1–3 h	8–24 h	4–7 h	2–6 h	3–6 h
Protein bound (%)	93	50–65	—	98	—	87	70–80
Volume of distribution (L/kg)	1.8–4.6	>100	3	15–40	>100	3	0.5–1
Half-life	9–15 h	40–55 d	5–7 h	15–27 d	1–6 d	3–4 d	21–30 h
Urinary excretion (%)	20	55	4	<1	—	16–32	20

scotomata, and sometimes complete blindness because of the direct toxicity. Onset of blindness is invariably delayed and usually follows the onset of other manifestations by at least 6 hours. Funduscopic examination may be normal but usually demonstrates extreme arteriolar constriction associated with optic disc and retinal edema. Improvement in vision may occur rapidly, but is usually slow, occurring over a period of months after a severe exposure. Initially, improvement occurs centrally and is followed later by improvement in peripheral vision. The pupils may remain dilated even after return to normal vision. Those with the greatest exposure may develop optic atrophy.

Eighth-nerve dysfunction results in tinnitus and deafness. This causes a rapid decrease in auditory acuity with a flattening of audiograms. These findings usually resolve within 48–72 hours, and permanent hearing impairment is unlikely.

Hemolysis may also occur in patients with glucose-6-phosphate dehydrogenase deficiency.

Hypersensitivity reactions result from antiquinine or antiquinine–hapten antibodies cross-reacting with a variety of membrane glycoproteins. Asthma sometimes occurs. Dermatologic manifestations include urticaria, photosensitivity dermatitis, cutaneous vasculitis, lichen planus, and angioedema. Hematologic manifestations of hypersensitivity are rare, but include thrombocytopenia, agranulocytosis, microangiopathic hemolysis, and disseminated intravascular coagulation (DIC), which can lead to jaundice, hemoglobinuria, and renal failure. Hepatitis is a rare hypersensitivity reaction. Acute respiratory distress syndrome (ARDS) and a sepsislike syndrome are reported.

Diagnostic Testing

Urine thin-layer chromatography is sensitive enough to confirm the presence of quinine even following the ingestion of tonic water. Immunoassay techniques are the most reliable, but quantitative plasma testing is not rapidly or widely available. Quinidine immunoassays cannot be substituted. Although no specific plasma drug concentration determines a unique management intervention, plasma quinine concentrations are prognostic. Levels greater than 10 μg/mL are associated with temporary blindness, and levels of 15 μg/mL are associated with increased risk of permanent visual damage, dysrhythmias, and death.

Management

Emetic agents should not be used, as seizures, dysrhythmias, and hypotension may also develop rapidly. Orogastric lavage should only be performed for patients with recent and substantial ingestions and no spontaneous emesis. Otherwise, activated charcoal (1 g/kg), and supportive techniques such as oxygen, cardiac monitoring, an IV access, volume resuscitation, and dextrose support are indicated as needed.

The sodium channel manifestations of quinine cardiotoxicity should be treated with serum alkalinization. Patients with a prolonged QRS complex or heart block should be given hypertonic sodium bicarbonate to achieve a serum pH of 7.45–7.50, as would be done in the presence of a patient with a serious cyclic antidepressant overdose. Unfortunately, this therapy may produce hypokalemia, potentially exacerbating the effect of potassium channel blockade. Consequently, the QTc should be carefully monitored for prolongation. Interventions for torsades de pointes, including magnesium administration, potassium supplementation, and overdrive pacing, may be necessary.

Class IA, IC, or III antidysrhythmics, those with sodium channel and/or potassium channel blocking activity, should not be used because they may exacerbate the toxin-related conduction disturbances or dysrhythmias. Type IB antidysrhythmics might be useful if other therapies fail.

Serum glucose should be initially supported with an adequate infusion of dextrose. Subcutaneous octreotide, 50–100 μg in adults and 1–1.5 μg/kg in children, blocks insulin secretion, and should be used for recurrent hypoglycemia.

Multiple-dose activated charcoal significantly decreases quinine half-life. Activated charcoal (0.5–1 g) should be administered orally every 2–4 hours as long as toxicity persists. Because quinine has a relatively large volume of distribution and is highly protein bound to plasma albumin and α_1-acid glycoprotein, peritoneal dialysis, hemoperfusion, hemodialysis, and exchange transfusion have a limited effect on drug removal and are not routinely recommended.

CHLOROQUINE, HYDROXYCHLOROQUINE, AND AMODIAQUINE

Pathophysiology

Like quinine, chloroquine has a small toxic-to-therapeutic margin. Severe chloroquine poisoning is usually associated with ingestions of 5 g or more, or with serum concentrations exceeding 5 μg/mL. The cardiovascular effects of chloroquine and hydroxychloroquine are similar to those of quinine, but other features, including cinchonism, are uncommon. Visual changes are not described with prophylactic doses but occur rarely with daily dosing of chloroquine or hydroxychloroquine for arthritis.

Clinical Manifestations

Because chloroquine is rapidly absorbed from the GI tract, symptoms are usually noted within 1–3 hours. Apnea, hypotension, and cardiovascular compromise can be precipitous. CNS depression, dizziness, headache, and convulsions also occur. Electrocardiographic abnormalities include QRS prolongation, atrioventricular (AV) block, ST-T depression, increased U waves, and QTc prolongation, but these are less frequent than with quinine. Significant hypokalemia is invariably associated with the cardiac manifestations. Hypokalemia results from chloroquine-induced intracellular shifts. Hemolysis may occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Acute hydroxychloroquine toxicity is similar to chloroquine toxicity. Side effects in routine dosing include nausea and abdominal pain, hemolysis in G6PD-deficient patients, and, rarely, retinal damage, sensorineural deafness, and hypoglycemia.

Although there is no overdose experience reported, 1 report of amodiaquine toxicity suggests that neurologic toxicity, including involuntary movements, muscle stiffness, dysarthria, syncope, and seizures, may occur.

Management

Early, aggressive management of severe chloroquine toxicity is documented to decrease the fatality rate. The protocol involves the use of epinephrine for chloroquine-related vasodilation and myocardial depression and diazepam for possible direct cardiovascular effect and for sedation. Patients should receive early endotracheal intubation and mechanical ventilation. Orogastric la-

vage should be performed on patients with recent and substantial ingestions and activated charcoal should be administered. During decontamination, 2 mg/kg of IV diazepam is given over 30 minutes and then 1–2 mg/kg/d for 2–4 days. Simultaneously, epinephrine (0.25 μg/kg/min) should be given IV with 5% dextrose in water (D_5W), adjusted incrementally until a systolic blood pressure over 100 mm Hg is achieved. Even after this initial therapy, some patients may manifest transient cardiovascular compromise and require additional epinephrine and other catecholamines. Serum potassium concentrations should be monitored and potassium supplementation administered. Aggressive replacement therapy is not encouraged because hypokalemia represents intracellular shift, not total-body potassium depletion. Although sound data are lacking, severe hydroxychloroquine cases should be treated similarly. Because chloroquine and hydroxychloroquine have a high volume of distribution, significant protein binding, and a long terminal elimination half-life, enhanced elimination procedures are not beneficial.

PRIMAQUINE

Clinical Manifestations

Primaquine causes red blood cell (RBC) oxidant stress. Methemoglobinemia and hemolysis can occur in normal individuals given high doses. Overdose with primaquine occurs rarely. Nausea, headache, and abdominal cramps are described. Extreme iatrogenic overdose results in hallucinations, abdominal cramps, nausea, jaundice, hepatitis, and black urine. Resolution occurs over 1 month.

Management

In the event of overdose, therapy should be directed at minimizing absorption with activated charcoal and reversing significant methemoglobinemia with methylene blue (see Antidotes in Brief: Methylene Blue).

MEFLOQUINE

Clinical Manifestations

Common effects include nausea, vomiting, and diarrhea. Mefloquine also has a mild cardiodepressant effect, less than that of quinine or quinidine. With prophylactic use, neither the PR interval nor the QRS complex is prolonged, but the QTc interval may be prolonged. Clinically, insignificant bradycardia is common. During prophylactic use, many patients experience insomnia and an alteration in dreams and complain of dizziness, headache, fatigue, mood alteration, and vertigo. Seizures occur very rarely in prophylaxis and therapeutic use.

Overdose data are sparse, but symptoms include confusion, agitation, ataxia, dizziness, speech difficulties, high-frequency hearing loss, nausea, fatigue, weakness, depression, disorientation, and paresthesia. Mild hypotension, tachycardia with occasional ventricular premature complexes, minimal increases in liver function tests, and prolonged prothrombin time (PT) are also reported.

Management

Decontamination with activated charcoal is indicated if the patient presents soon after the ingestion. Hemodialysis does not remove mefloquine.

HALOFANTRINE

Clinical Manifestations

The primary toxicity in therapeutic and supratherapeutic doses is prolongation of the QTc, producing torsades de pointes and ventricular fibrillation. Palpitations, hypotension, and syncope may occur. First-degree heart block is common but bradycardia is rare. Because the QTc is directly related to serum concentration, dysrhythmias would be expected to be more common in overdose. Dysrhythmias are also likely in the context of combined overdose or combined/serial therapeutic use with other drugs that cause QTc prolongation, particularly mefloquine.

Other side effects, including nausea, vomiting, diarrhea, abdominal cramping, headache, and lightheadedness, which occur frequently in therapeutic use, are expected in overdose. Less frequently described side effects, such as pruritus, myalgia, and rigors, may also occur. In a very few patients, seizures, minimal liver enzyme elevation, and hemolysis are described.

Management

Management of halofantrine overdose should focus on GI decontamination, general supportive care, and cardiac monitoring for QTc prolongation and associated dysrhythmias. Treatment of prolonged QTc and torsades de pointes is as discussed under quinine.

PROGUANIL, PYRIMETHAMINE, SULFADOXINE, DAPSONE, AND ATOVAQUONE

Pharmacokinetics and Toxicodynamics

Proguanil, pyrimethamine, sulfadoxine, and dapsone all interfere with folate metabolism and are usually used in combination. Proguanil (chlorguanide) may be used alone but is often used with dapsone (Lapdap), chloroquine, or the antiparasitic atovaquone (Malarone) for prophylaxis. Atovaquone inhibits the de novo pyrimidine synthesis necessary for protozoal survival and replication, but unnecessary in mammalian cells.

Clinical Manifestations

Information on proguanil overdose is limited. Proguanil's side effects during prophylaxis include nausea, diarrhea, and mouth ulcers. Because of folate interference, megaloblastic anemia is a rare complication. Rarely, neutropenia, thrombocytopenia, rash, and alopecia are also noted. In a single case report, hypersensitivity hepatitis was described. When used to treat malaria, atovaquone/proguanil causes vomiting, which is sometimes severe, in 15–45% of patients. The combination is associated with elevated liver function tests.

Atovaquone alone is relatively well tolerated. Side effects include maculopapular rash, rarely erythema multiforme, GI complaints, and a mild increase in aminotransferases. Three cases of 3–42-fold overdose or excess dosing are reported. No symptoms occurred in one case (at 3 times therapeutic serum concentrations), rash occurred in another, and in the third, methemoglobinemia was attributed to a simultaneous overdose of dapsone.

Dapsone and the sulfonamides have a long history of causing idiosyncratic reactions, including neutropenia, thrombocytopenia, eosinophilic pneumonia, aplastic anemia, neuropathy, and hepatitis. The rare occurrence of life-threat-

ening erythema multiforme major associated with pyrimethamine-sulfadoxine prophylaxis has limited the use of this combination for prophylaxis.

Acute ingestion of dapsone may result in nausea, vomiting, and abdominal pain. Following overdose, dapsone produces RBC oxidant stress, leading to methemoglobinemia and, to a much lesser extent, sulfhemoglobinemia. The onset of hemolysis may be immediate or delayed. Other symptoms, particularly cardiac and neurologic symptoms, resulting from end-organ hypoxia, may occur, but are uncommon. In addition, in overdose, hepatitis and neuropathy are described.

Overdose of pyrimethamine alone is rare. In children, it results in nausea, vomiting, rapid onset of seizures, fever, and tachycardia. Blindness, deafness, and mental retardation have followed. Seizures were attributed to a 12-tablet overdose of sulfadoxine-pyrimethamine taken over 2 days. Chronic high-dose use may be associated with a megaloblastic anemia, requiring folate replacement.

Management

Folate supplementation (50 mg in adults or 1 mg/kg in children) should be given after overdose of proguanil or pyrimethamine. Other efforts should include supportive care. Significant methemoglobinemia should be treated with methylene blue (1 mg/kg IV). In addition, cimetidine may be used to prevent conversion of dapsone to its toxic metabolite. Multiple-dose activated charcoal (0.5–1 g/kg repeated every 2–4 hours) enhances elimination of dapsone.

ARTEMISININ AND DERIVATIVES

Pharmacokinetics and Toxicodynamics

Artemisinin and its derivatives (artemether, arteether, dihydroartemesinin, and artesunate) come from the Chinese herb qinghaosu. They were introduced in the 1980s in China for the treatment of malaria. Millions of doses of artemisinin and its derivatives have been used in Asia and Africa.

The parent drug has poor solubility and limited bioavailability. Derivatives have greater absorption and some may be used parenterally, but are rapidly degraded. Artesunate has the longest half-life. Because these drugs have a short half-life, prolonged courses of therapy are required to prevent recrudescence of malaria. To provide a shorter, more effective treatment and to reduce the emergence of malarial resistance, artemisinins are frequently used in combination with mefloquine. Recently the oral combination drug artemether-lumefantrine was introduced.

The efficacy and toxicity of artemisinin is thought to be a result of the ability of the trioxane molecular core to form intracellular free radicals, particularly in the presence of heme. In animals, damage to brainstem nuclei is consistently produced following prolonged, high-dose and parenteral administration.

Clinical Manifestations

In contrast, human experience in more than 8000 study participants shows these medications to have a very low incidence of side effects. Low-frequency side effects include nausea, vomiting, abdominal pain, diarrhea, and dizziness. Prospective studies have failed to identify any adverse neurologic outcome. Rare reports of CNS side effects during therapeutic use suggest the possibility of CNS depression, seizures, or cerebellar symptoms following intentional self-poisoning.

In patients receiving serial ECGs, a small, but statistically significant, fall in heart rate is noted coincident with peak drug concentrations. In one therapeutic trial, 7% of adult patients receiving artemether had an asymptomatic QTc prolongation of at least 25%, but changes in the QRS were not noted.

There is little experience with the toxicity of lumefantrine alone. It is related to mefloquine and halofantrine. The combination product is well tolerated. Studies of the combination product artemether-lumefantrine have not shown prolongation in QTc or cardiac toxicity related to lumefantrine. Cough and angioedema were described in one case.

Management

Overdose patients should be managed with supportive measures and expectant observation, including cardiovascular monitoring. CNS manifestations are the most likely.

57 | Anticoagulants

HISTORY AND EPIDEMIOLOGY

As early as the late 19th century, human urine was noted to have proteolytic activity with a specificity for fibrin. A substance found to be an activator of endogenous plasminogen was isolated, purified, and given the name *urokinase*. The discovery of modern-day oral anticoagulants originated following investigations of a hemorrhagic disorder in cattle in the early 20th century. The hemorrhagic agent, eventually identified as bishydroxycoumarin, would be the precursor to warfarin.

The diversity of these anticoagulant and fibrinolytic agents has led to ever-increasing use in many fields of medicine. Warfarin is the most common oral anticoagulant in use today because of its use in patients with cerebrovascular disease, cardiac dysrhythmias, and thromboembolic disease. The common problem of excessive warfarin effects leading to hemorrhage is poorly quantitated as an adverse drug event and frequently goes untabulated. Adverse drug events, prescribing errors, and drug interactions plague the use of heparins, thrombolytics, and warfarin. Unintentional ingestion of warfarin or superwarfarin rodenticides is a common problem in children and animals.

PHYSIOLOGY

An understanding of the normal function of the coagulation pathways is essential to appreciate the etiology of a coagulopathy. The critical steps of the coagulation cascade are summarized here. Chapter 24 has additional details. Coagulation consists of a series of events that prevent excess blood loss and assist in the restoration of blood vessel integrity. Within the cascade, coagulation factors exist as inert precursors and are transformed into enzymes when activated. Activation of the cascade occurs through one of two distinct pathways, the intrinsic and extrinsic systems (Fig. 57–1). Once activated, these enzymes catalyze a series of reactions that ultimately converge and lead to the generation of thrombin and the formation of a fibrin clot. Antithrombin III, protein C, and protein S serve as inhibitors, maintaining the homeostasis that is required to prevent spontaneous clotting and keep blood fluid. Protein C, when aided by protein S, inactivates 2 plasma factors, V and VIII. Antithrombin III complexes with all the serine protease coagulation factors (factor Xa, factor IXa, and contact factors, including XIIa, kallikrein, and high-molecular-weight kininogen) except factor VII. Thrombolytics such as streptokinase, urokinase, anistreplase, tenecteplase, and recombinant tissue plasminogen activator (rt-PA) enhance the normal processes that lead to clot degradation.

DEVELOPMENT OF COAGULOPATHY

Impaired coagulation results from decreased production or enhanced consumption of coagulation factors, the presence of inhibitors of coagulation, ac-

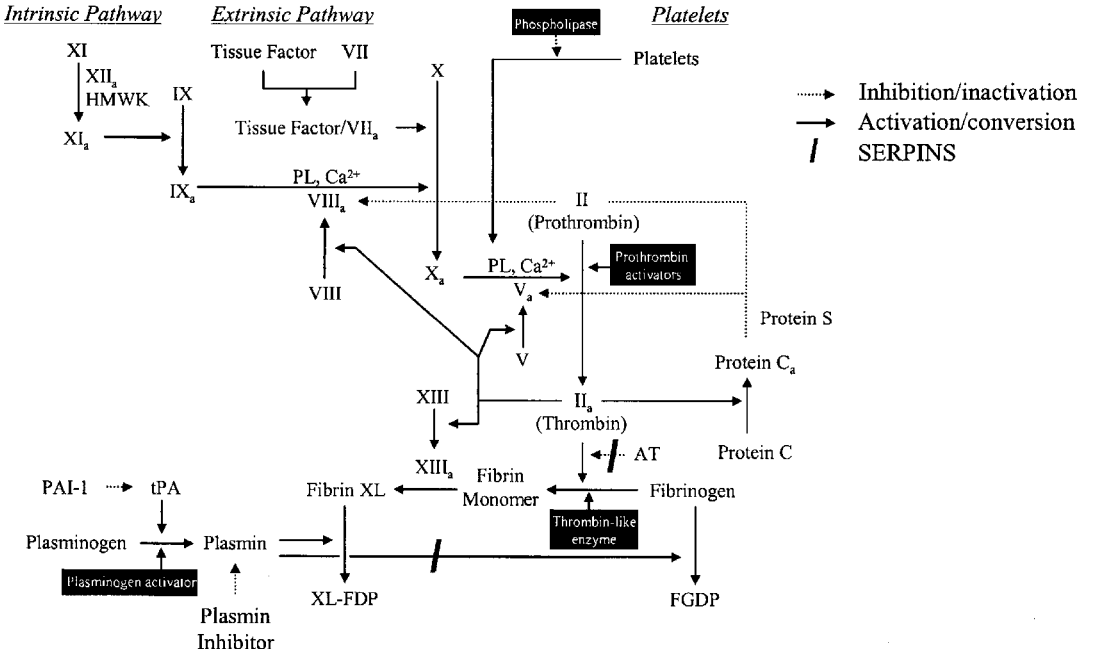


FIG. 57–1. The figure presents a schematic overview of the coagulation and fibrinolytic pathways and indicates where phospholipids on the platelet surface interact with the coagulation pathway intermediates. Arrows are not shown from platelets to phospholipids involved in the tissue factor VII_a and the factor IX_a–$VIII_a$ interactions to avoid confusion. Interactions of selected venom proteins are indicated in the black boxes. The diagram is not complete with reference to the multiple sites of interaction of the SERPINS (serine protease inhibitors) to avoid overcrowding. PL = platelets; XL = cross-linked.

tivation of the fibrinolytic system, or abnormalities in platelet number or function. Chapter 24 discusses platelet-related abnormalities.

Decreased production of coagulation factors results from congenital and acquired etiologies. Although congenital disorders of factor VIII (hemophilia), factor IX (Christmas factor), factor XI, and factor XII (Hageman factor) are all reported, their overall incidence is still quite low. Factors II, V, VII, and X are entirely synthesized in the liver; thus hepatic dysfunction is one of the most common causes of acquired coagulopathy. In addition, factors II, VII, IX, and X require postsynthetic activation by an enzyme that uses vitamin K as a cofactor, such that vitamin K deficiency (from malnutrition, changes in gut flora secondary to xenobiotics, or malabsorption) or inhibition of vitamin K cycling (from warfarin, as will be described) is capable of impairing coagulation. Excessive consumption of coagulation factors usually results from massive activation of the coagulation cascade as occurs in severe hemorrhage or disseminated intravascular coagulation.

ORAL ANTICOAGULANTS

Warfarin and "Warfarinlike" Anticoagulants

The mechanism of action of warfarin and warfarinlike anticoagulants involves vitamin K cycle inhibition. Vitamin K is a cofactor in the postribosomal synthesis of clotting factors II, VII, IX, and X (Fig. 57–2). The vitamin K–sensitive enzymatic step that occurs in the liver involves the γ-carboxylation of 10 or more glutamic acid residues at the amino terminal end of the precursor proteins. The carboxylation activity is coupled to an epoxidase activity for vitamin K, whereby vitamin K is oxidized to vitamin K 2,3-epoxide. This inactive form of the vitamin is converted to the active form by two successive reductions. Warfarin and all warfarinlike compounds inhibit the activity of vitamin K 2,3-epoxide reductase and vitamin K quinone reductase, which subsequently inhibits the formation of activated clotting factors.

Pharmacology of Warfarin

Orally ingested warfarin is virtually completely absorbed and peak plasma concentrations occur approximately 3 hours after drug administration. Because only the free warfarin is active, drugs that compete for binding to albumin or inhibit warfarin metabolism may markedly influence the anticoagulant effect (Table 57–1). Because vitamin K turnover is rapid, the anticoagulant effect is dependent on factor half-life ($t_{1/2}$), with factor VII ($t_{1/2}$ ~5 hours) depleted most rapidly. For a prolongation of the international normalized ratio (INR) to occur, factor concentrations must fall to approximately 25% of normal values. This suggests that in patients who are not originally anticoagulated, at least 15 hours (3 factor VII half-lives) are required before warfarin's effect is evident. In fact, complete inhibition does not occur in this time frame, causing the onset of coagulation to be delayed even further.

The half-life of warfarin in humans is 40 hours; thus its duration of action may be up to 5 days. R-Warfarin is metabolized by isozymes CYP1A2 and CYP3A4, and S-warfarin is metabolized by isozyme CYP2C9 of the hepatic microsomal P450 enzyme system. S-Warfarin is more potent.

Pharmacology of Long-Acting Anticoagulants

There are two 4-hydroxycoumarin derivatives—difenacoum and brodifacoum—that differ from warfarin by their longer, higher-molecular-weight polycyclic hydrocarbon side chain. Together with a third agent, chlorophacinone, they are

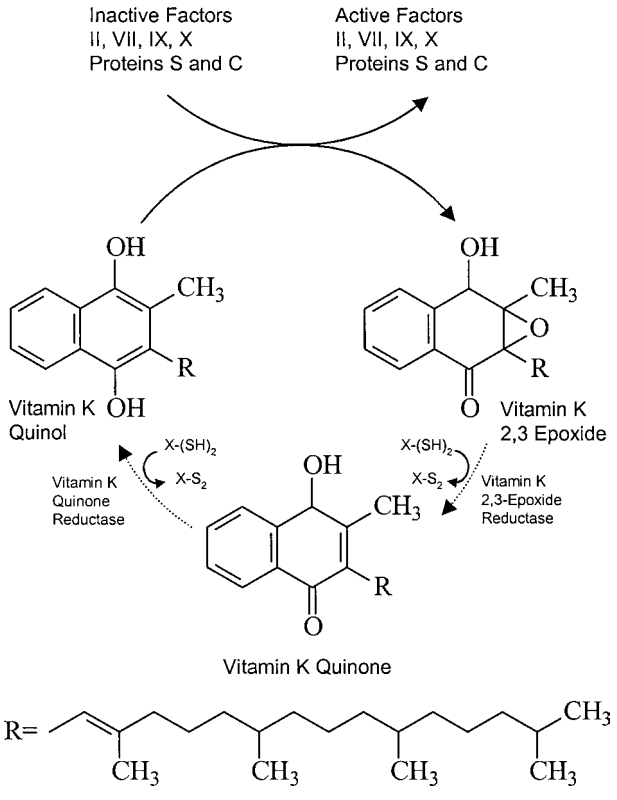


FIG. 57–2. The vitamin K cycle. Dotted lines represent pathways that can be blocked with warfarin and warfarinlike anticoagulants. The aliphatic side chain (R) of vitamin K_1 is shown below the metabolic pathway.

known as "superwarfarins," or long-acting anticoagulants. Long-acting anticoagulants were designed to be effective rodenticides in warfarin-resistant rodents. Their mechanism of action is identical to that of the traditional warfarinlike anticoagulants, but they are 100 times more potent than warfarin and have a longer duration of action. Many cases of intentional overdose of long-acting anticoagulants in humans are also described in the literature. These patients' clinical courses are characterized by a severe coagulopathy that may last weeks to months, often accompanied by consequential blood loss. Patients with unintentional ingestions must be distinguished from those with intentional ingestions, because the former individuals demonstrate a low likelihood of producing coagulation abnormalities and have only rare morbidity or mortality. Prolongation of the INR is unlikely with a single, small ingestion of a superwarfarin rodenticide. Clinically significant anticoagulation is even rarer. Most patients (usually children) are entirely asymptomatic and have a normal coagulation profile following an acute unintentional exposure. Knowing that the risk of coagulopathy is low and that it takes days to develop, most authors recommend supportive care only. Despite the fact that significant

TABLE 57–1. Common Drug Interactions with Warfarin Anticoagulation

Potentiation		Antagonism
Acetaminophen	Isoniazid	Antacids
Allopurinol	Ketoconazole	Barbiturates
Amiodarone	Metronidazole	Carbamazepine
Anabolic steroids	Nonsteroidal anti-	Cholestyramine
Aspirin	inflammatory drugs	Colestipol
Carbenicillin	Omeprazole	Corticosteroids
Clarithromycin	Phenytoin	Griseofulvin
Cephalosporins	Propafenone	Oral contraceptives
Chloral hydrate	Propoxyphene	Phenytoin
Cimetidine	Quinidine	Rifampin
Clofibrate	Quinolones	Vitamin K
Cyclic antidepressants	Sulfonylureas	
Disulfiram	Tamoxifen	
Erythromycin	Tetracycline	
Ethanol	Thyroxine	
Fluconazole	Trimethoprim-	
HMG-CoA reductase	sulfamethoxazole	
inhibitors	Vitamin E	

toxicity is indeed rare from superwarfarins, it should be recognized that the reported benign courses of pediatric exposures may be misleading. Multiple retrospective studies suggest that children with unintentional acute exposures do not require any followup coagulation studies. There are clearly insufficient data to justify this conclusion as many of these "exposed" children were never documented to have ingested long-acting anticoagulants. We recommend that clinicians continue to manage these children as possible exposures and that all children be followed up with daily INR studies for at least 48 hours.

Clinical Manifestations

Typical warfarin-containing rodenticides contain only small concentrations (0.025% or 25 mg of warfarin per 100 g of product) of anticoagulant. A 10-kg child would require an initial dose of 2.5 mg of warfarin for therapeutic anticoagulation (or 10 g of rodenticide). These quantities are far greater than those that occur in typical "tastes." Thus, single unintentional ingestions of warfarin-containing rodenticides pose virtually no threat and require no therapy. In contrast, intentional and large unintentional ingestions of pharmaceutical-grade anticoagulants have the potential to produce a coagulopathy and consequential bleeding. Patients present with typical manifestations of impaired coagulation: bruising, hematuria, hematochezia, and menorrhagia. Hemorrhage into the neck with resultant airway compromise is a rare but life-threatening complication. The most serious complication of excessive anticoagulation is intracranial hemorrhage, which is reported to occur in as many as 2% of patients on long-term therapy.

Although intentional ingestions of warfarin-containing products are uncommon, adverse drug events resulting in excessive anticoagulation and bleeding frequently occur. The Outpatient Bleeding Risk Index is based on 4 independent risk factors, age 65 years or older; history of cerebrovascular accident; history of gastrointestinal bleeding; or history of recent myocardial infarction, hematocrit <30%, serum creatinine >1.5 mg/dL, or diabetes mellitus. The sum of the number of risk factors successfully predicted major

bleeding at 48 months to be 3% in low-risk (0 risk factors), 12% in intermediate-risk (1–2 risk factors), and 53% in high-risk (3–4 risk factors) patients.

Laboratory Assessment

Established screening tests are helpful for diagnosis. Four studies—prothrombin time (PT) (INR), partial thromboplastin time (PTT), thrombin time, and fibrinogen concentration—are usually adequate. In patients taking oral anticoagulants, the INR is extremely effective at monitoring the extent of anticoagulation. However, in patients with acute fulminant hepatic failure of various etiologies, the INR is extremely variable and occasionally misleading, so most studies still use the PT. The PTT is not affected by alterations in factors VII, XIII, or platelets. The thrombin time evaluates the ability to convert fibrinogen to fibrin and is thus unaffected by abnormalities of factors II, V, VII to XIII, platelets, prekallikrein, or high-molecular-weight kininogen (HMWK). Finally, either a fibrinogen concentration or a determination of fibrin degradation products will help distinguish between problems with clot formation and consumptive coagulopathy. An evaluation of the combination of normal and abnormal results of these tests usually determines a patient's clotting abnormality (Table 57–2).

Although warfarin concentrations may be useful to confirm the diagnosis in unknown cases and to study drug kinetics, the routine use of simple and inexpensive measures such as INR determination seems more appropriate.

TABLE 57–2. Evaluation of Abnormal Coagulation Times

PT normal, PTT prolonged, bleeding
Deficiencies of factors VIII, IX, XI
Von Willebrand disease
PT normal, PTT prolonged, no bleeding
Deficiencies of factor XII, prekallikrein, high-molecular-weight kininogen inhibitor syndrome
PT prolonged, PTT normal
Deficiency of factor VII
Warfarin therapy (early)
Vitamin K deficiency (mild)
Liver disease (mild)
PT and PTT prolonged, thrombin time normal, fibrinogen normal
Deficiencies of factors II, V, IX; vitamin K deficiency (severe)
Warfarin therapy (late)
PT and PTT prolonged, thrombin time abnormal, fibrinogen normal
Heparin effect
Dysfibrinogenemia
PT and PTT prolonged, thrombin time abnormal, fibrinogen abnormal
Liver disease
Disseminated intravascular coagulation
Fibrinolytic therapy
Crotaline envenomation

Laboratory Evaluation of Long-Acting Anticoagulants

For patients who have ingested long-acting anticoagulants and are considered unlikely to develop a coagulopathy, baseline studies can be avoided. Serial INRs at 24 and 48 hours should identify all patients at risk of coagulopathy. Depending on the social situation, these studies can be obtained while the patient remains in the home setting. In contrast, all patients with intentional ingestions of long-acting anticoagulants should be presumed to be at risk for a severe coagulopathy. In fact, most patients do not seek medical care until bruising or bleeding is evident. Because bleeding occurs many days after ingestion, gastric decontamination is useless unless repetitive ingestion is suspected. Daily or twice-daily INR evaluations for 2 days should be adequate to identify most patients at risk for coagulopathy. Early detection through coagulation factor analysis may be preferred, however, and concentrations of long-acting anticoagulants can now be measured.

General Management and Antidotal Treatment

For patients who present a few hours after ingestion, gastric emptying is not indicated (Chap. 8). At least a single dose of activated charcoal should be administered unless it is contraindicated. Oral cholestyramine can also be considered to enhance warfarin elimination, but strong supportive data are lacking. In addition to general supportive measures, the patient should be placed in a supervised medical and psychiatric environment that offers protection against external or self-induced trauma, and permits observation for the onset of coagulopathy.

Blood transfusion is required for any patient with a history of blood loss or active bleeding who is hemodynamically unstable, has impaired oxygen transport, or is expected to become unstable. Although a transfusion of packed red blood cells is ideal for replacing lost blood, it cannot correct a coagulopathy, and thus patients will continue to bleed. Transfusion of whole blood may be considered in severe cases because whole blood contains many components, such as platelets, white blood cells, and non–vitamin K-dependent factors. However, because whole blood contains only relatively small amounts of vitamin K–dependent factors, selective use of specific blood products is generally preferred. These include packed red blood cells, fresh-frozen plasma (FFP), cryoprecipitate, or other factor concentrates, such as factor IX complex, recombinant factor VIIa (rFVIIa), and prothrombin complex concentrate.

Life-threatening hemorrhage secondary to oral anticoagulant toxicity should be immediately reversed with FFP, followed by vitamin K_1. Vitamin K_1 is preferable over the other forms of vitamin K (see Antidotes in Brief: Vitamin K). In general, approximately 15 mL/kg of FFP should be adequate to reverse warfarin-induced coagulopathy. However, the specific factor quantities and volume of each unit may be varied, leading to an unpredictable response. Furthermore, multiple FFP transfusions may also be required because of the rapid degradation of coagulation factors in the absence of vitamin K. Preliminary data using rFVIIa demonstrate it to be a useful pharmacologic therapy for bleeding secondary to warfarin-induced excessive anticoagulation.

Several issues influence the decision to administer vitamin K_1 to a patient with a suspected overdose of a warfarinlike anticoagulant. Answers to the following questions should always be considered. Does the ingestion involve a warfarin-containing rodenticide or a pharmaceutical preparation? Is the ingestion unintentional or intentional? Does the patient require maintenance of therapeutic anticoagulation? Moreover, although vitamin K_1 administration is

required to reverse the blockade of coagulation factor activation, it cannot be relied upon for the patient with acute and consequential hemorrhage (see Antidotes in Brief: Vitamin K_1), as it takes several hours to activate enough factors to reverse the coagulopathy.

If complete reversal of INR prolongation occurs or is desirable (as in most cases of life-threatening bleeding), and the patient's underlying medical condition still requires some degree of anticoagulation, the individual can receive controlled anticoagulation with heparin until the bleeding is controlled and the patient is otherwise stable. In a patient not requiring chronic anticoagulation, even small elevations of the INR may be treated (with vitamin K_1 alone) to prevent a deterioration in coagulation status and reduce the risk of bleeding. For a patient requiring chronic anticoagulation, The American College of Chest Physicians has issued guidelines for management of patients with elevated INRs (Table 57–3).

Treatment of Long-Acting Anticoagulant Overdoses

Treatment of long-acting anticoagulant overdose is essentially the same as the treatment of oral anticoagulant toxicity with certain exceptions. Prophylactic vitamin K_1 should not be administered as it will not prevent the eventual development of coagulopathy and will only interfere with the ability to

TABLE 57–3. Recommendations for Management of Elevated INR, with and without Bleeding, in Patients Requiring Chronic Anticoagulation[a]

INR	Recommendations
• <5.0; no significant bleeding	Lower dose or omit next dose of warfarin
• ≥5.0–9.0; no significant bleeding	Discontinue warfarin for several doses. Alternatively, omit next dose and give oral vitamin K_1 (1–2.5 mg) especially if at increased risk of bleeding. If more rapid reversal is necessary, give oral vitamin K_1 (≤5 mg) and wait 24 hours. Give additional vitamin K_1 orally (1–2 mg) as needed.
• ≥9.0; no significant bleeding	Hold warfarin therapy and give a higher dose of oral vitamin K_1 (5–10 mg) and wait 24 hours. Give additional vitamin K_1 if necessary.
• Serious bleeding at any concentration or life-threatening bleeding	Hold warfarin therapy and give vitamin K_1 (10 mg by slow parenteral[b] infusion) supplemented with fresh-frozen plasma or prothrombin complex concentrate; recombinant factor VIIa may be used instead of prothrombin complex concentrate. Vitamin K_1 administration may need to be repeated q12 h.

[a]If continued warfarin therapy is indicated after high doses of vitamin K_1, then anticoagulation with heparin or low-molecular-weight heparin (LMWH) can be concomitantly given. INR values >4.5 are also less reliable than values at or near the therapeutic range.

[b]Although parenteral infusion of vitamin K_1 is recommended, we urge caution with this route of administration because there may not be an appreciable difference in onset of therapeutic effect and, although rare, may cause severe anaphylactoid reactions.

Adapted from American College of Chest Physicians Consensus Conference 2004 guidelines.

determine if coagulopathy will develop. Once coagulopathy occurs, repetitive large doses of vitamin K_1 (on the order of 60 mg/d) may be required in some patients. A patient with a long-acting anticoagulant overdose should be followed until the coagulation studies remain normal while off therapy for several days. This may require weeks to months of close observation for both psychiatric and medical management.

PARENTERAL ANTICOAGULANTS

Heparin

Pharmaceutical heparins are extracted from bovine lung tissue and porcine intestines. Conventional, or unfractionated, heparin is a heterogeneous group of molecules that inhibit thrombosis by accelerating the binding of the protease inhibitor antithrombin III to thrombin (factor II) and other serine proteases involved in coagulation. Thus, factors IX to XII, kallikrein, and thrombin are inhibited. Heparin's therapeutic effect is usually measured through the activated PTT, although the activated blood coagulation time (ACT) may be more useful for monitoring large therapeutic doses or in the overdose situation.

Low-molecular-weight (LMW) heparins are 4000–6000-dalton fractions obtained from conventional (unfractionated) heparin that share many of the pharmacologic and toxicologic properties of conventional heparin. The major differences between LMW heparins and conventional heparin are greater bioavailability, longer half-life, incomplete reversal with protamine, more predictable anticoagulation with fixed dosing, and targeted activity against activated factor X, and less against activated factor II. As a result of this targeted factor X activity, LMW heparins have minimal effect on the activated PTT, thereby eliminating either the need for, or the usefulness of such monitoring.

Pharmacology

Because of the large size and negative charge of heparin, it is unable to cross cellular membranes. Following parenteral administration, heparin remains in the intravascular compartment, in part bound to globulins, fibrinogen, and low-density lipoproteins, resulting in a volume of distribution of 0.06 L/kg. Because of its rapid metabolism in the liver by a heparinase, heparin has a short duration of effect. Although the half-life of elimination is dose dependent and ranges from 1–2.5 hours, the duration of anticoagulant effect is usually reported as 1–3 hours. Renal failure prolongs the duration of effect. Low-molecular-weight heparins have longer durations of effect, permitting intermittent administration.

Clinical Manifestations

Intentional overdoses with heparin are rare. Most reported cases involve unintentional poisoning in hospitalized patients. These cases have involved the administration of large amounts of heparin as a consequence of misidentification of heparin vials, during the process of flushing intravenous lines, and secondary to intravenous pump malfunction. Significant bleeding complications and death can occur. Although no overdoses of LMW heparins are reported, LMW heparins are renally eliminated, and patients with severe renal insufficiency (creatinine clearance <30 mL/min) or end-stage renal disease are at increased risk of toxicity. Similar adverse effects to unfractionated heparins are also reported to include epidural/spinal hemato-

mas, intrahepatic hemorrhage, abdominal wall hematomas, and intracranial hemorrhage.

Evaluation and Treatment

After stabilization of the airway, breathing, and circulation are assured, the physician should be prepared to replace blood loss and reverse the coagulopathy, if indicated. Because of the relatively short duration of action of heparin, observation alone may be indicated if significant bleeding has not occurred. For the patient requiring anticoagulation, serial PTT determinations will indicate when it is safe to resume therapy. If significant bleeding occurs, either removal of the heparin or reversal of its anticoagulant effect is indicated. Because heparin has a very small volume of distribution, it can be effectively removed by exchange transfusion. Although this technique has been used successfully in neonates, it is not generally applicable to older children and adults. When severe bleeding occurs, heparin may be effectively neutralized by protamine sulfate (see Antidotes in Brief: Protamine). Protamine forms ionic bonds with heparin and renders it devoid of anticoagulant activity. One milligram of protamine sulfate injected intravenously neutralizes 100 units of heparin. The dose of protamine should be calculated from the dose of heparin administered, if known, and assuming the approximate half-life of heparin to be 60 minutes, such that the amount of protamine does not exceed the amount of heparin expected to be found intravascularly at the time of infusion. Because approximately 0.2% of patients receiving protamine experience anaphylaxis, a complication that carries a 30% mortality rate, most authors commonly recommend that protamine be reserved for patients with life-threatening hemorrhage. It should also be noted that excess protamine administration may result in paradoxical anticoagulation.

If life-threatening bleeding occurs following LMW heparin administration, patients should be treated supportively. Protamine is only partially effective at reversing the effects of LMW heparin. In one report, activated factor VII effectively reversed bleeding from LMW heparin.

NONBLEEDING COMPLICATIONS OF ANTICOAGULANTS

Warfarin therapy is associated with three nonhemorrhagic lesions of the skin: urticaria, purple toe syndrome, and warfarin skin necrosis. Warfarin skin necrosis is linked, in part, to protein C deficiency. Protein C is also dependent on vitamin K. Because the half-life of protein C is shorter than that of many of the vitamin K–dependent coagulation factors, protein C levels fall rapidly during the first hours of warfarin therapy. In the protein C–deficient patient, protein C levels fall dramatically prior to a reduction in coagulation factors. This results in an imbalance that actually favors coagulation, and skin necrosis results because of microvascular thrombosis in dermal vessels. If necrosis occurs, warfarin should be discontinued and heparin should be initiated. The purple toe syndrome results from small atheroemboli that are no longer adherent to their plaques by clot.

Heparin therapy is associated with a transient and mild thrombocytopenia called heparin-induced thrombocytopenia (HIT) that occurs in approximately 25% of patients during the first few days of therapy. A more severe form of thrombocytopenia, heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) (formerly known as HIT-2 or the white clot syndrome), occurs in 1–5% of patients between days 7 and 14 of therapy, and even earlier in pa-

tients previously treated with heparin. Heparin stimulates platelets to release platelet factor 4, which subsequently complexes with heparin to provoke an IgG response. These antibodies against the heparin–platelet factor 4 complex activate platelets that may lead to platelet–fibrin thrombotic events. Patients may present with either hemorrhagic or thromboembolic complications.

FIBRINOLYTIC AGENTS AND OTHER ANTICOAGULANTS

Thrombolytics

The fibrinolytic system is designed to remove unwanted clots and to leave intact those clots that are protecting sites of vascular injury. Plasminogen exists as a proenzyme and is converted to the active form, plasmin, by various plasminogen activators. Tissue plasminogen activator (t-PA) is released from the endothelium and is under the inhibitory control of two inactivators known as tissue plasminogen activator inhibitors 1 and 2 (t-PAI-1 and t-PAI-2). The actions of plasmin are nonspecific in that it degrades not only fibrin clots but also some plasma proteins and coagulation factors.

Although all thrombolytics enhance fibrinolysis, they differ in their specific sites of action and durations of effect. Alteplase (t-PA) is specific for clot (it does not increase fibrinolysis in the absence of a thrombus), whereas streptokinase, urokinase, and anistreplase are not clot-specific. Alteplase has the shortest half-life and duration of effect (5 minutes and 2 hours, respectively), and anistreplase the longest (90 minutes and 18 hours, respectively). Streptokinase has the additional risk of severe allergic reaction on rechallenge, limiting its use to once in a lifetime. Newer thrombolytics, such as reteplase and tenecteplase, have a longer half-life in plasma and may be administered via single or repeated bolus injections.

Although the incidence of bleeding requiring transfusion may be as high as 7.7% following high-dose (150 mg) alteplase and 4.4% following low-dose alteplase, the incidence of intracranial hemorrhage with alteplase appears to be similar to the newer agents (monteplase, tenecteplase, reteplase, and lanoteplase). The addition of heparin to the thrombolytic regimen increases the risk of bleeding.

Supportive care is indicated for patients with minor bleeding complications; however, for patients with significant bleeding, fibrinogen and coagulation factor replacement with cryoprecipitate and FFP should be administered.

Snake Venoms

Chapter 117 discusses snake envenomations in detail. Snake venoms may be thought of as being procoagulant, anticoagulant, fibrinolytic, vessel wall interactive, platelet active, or as protein inactivators. Various mechanisms include individual factor activation, inhibition of protein C and thrombin, fibrinogen degradation, platelet aggregation, and inhibition of serine protease inhibitors (SERPINS).

Some of these venom proteins are being used as therapeutic agents for human diseases. Ancrod, a purified derivative of the Malayan pit viper, *Calloselasma rhodostoma* (formerly known as *Agkistrodon rhodostoma*), is used therapeutically because of its defibrinogenating property. The mechanism of action of ancrod and similar agents is to link fibrinogen end-to-end, subsequently preventing cross-linking. As expected, an increased risk of hemorrhage is observed; however, the risk appears to be less than that with thrombolytics. Moni-

toring of fibrinogen concentrations is essential to avoid potential complications as no specific antidote exists.

Hirudin

Hirudin is a polypeptide produced by the salivary glands of the medicinal leech (*Hirudo medicinalis*) that irreversibly blocks thrombin without the need for antithrombin III. Unlike heparin, the small size of hirudin allows it to enter clots and inhibit clot-bound thrombin, offering the distinct advantage of restricting further thrombus formation.

Vitamin K_1

Vitamin K_1 (phytonadione) is indicated for the reversal of elevated prothrombin times and international normalized ratios (INRs) in patients with xenobiotic-induced vitamin K deficiency. Vitamin K deficiency is typically induced following the therapeutic administration of warfarin or following the ingestion of the long-acting anticoagulant rodenticides (LAARs) such as brodifacoum.

CHEMISTRY

Vitamin K, an essential fat-soluble vitamin, is actually a broad term that encompasses at least two distinct natural forms. Vitamin K_1 (phytonadione, phylloquinone) is the only form synthesized by plants and algae. Most of the vitamin K ingested in the diet is vitamin K_1. Vitamin K_2 (menaquinones) is actually a series of compounds synthesized by bacteria.

DAILY REQUIREMENT

The human daily requirement for vitamin K is small; the Food and Nutrition Board set the recommended daily allowance at 1 μg/kg/d of phylloquinone for adults.

PHARMACOKINETICS OF DIETARY VITAMIN K

Dietary vitamin K in the form of phylloquinone and menaquinones is solubilized with the bile salts, free fatty acids, and monoglycerides to enhance absorption. Vitamin K, bound to chylomicrons, enters the circulation via the lymphatic system and then is taken up by the liver. In the plasma, vitamin K is primarily in the phylloquinone form, whereas liver stores are menaquinones and 10% phylloquinone.

PHARMACOLOGY

Activation of coagulation factors II, VII, IX, and X and proteins S and C requires α-carboxylation of the glutamate residues in a vitamin K–dependent process. Only the reduced (quinol, hydroquinone) form of vitamin K manifests biologic activity (Fig. 57–2). During the carboxylation step, the K quinol form is converted to an epoxide. This 2,3-epoxide is reduced and recycled to the active K quinol in a 2-step process that is inhibited by warfarin.

VITAMIN K DEFICIENCY AND MONITORING

Vitamin K deficiency can result from inadequate intake, malabsorption, or interference with the vitamin K cycle. Determination of vitamin K deficiency is usually established on the basis of a prolonged prothrombin time (PT), which is a surrogate marker of specific coagulation factors.

MECHANISM OF ACTION FOR XENOBIOTIC-INDUCED VITAMIN K DEFICIENCY

Oral anticoagulants are vitamin K antagonists that interfere with the vitamin K cycle, causing the accumulation of vitamin K 2,3-epoxide, an inactive

metabolite. Warfarin is a potent irreversible inhibitor of the dithiol-dependent vitamin K reductases (epoxide reductase and quinone reductase), which maintain vitamin K in its active (quinol, hydroquinone) form. The superwarfarins are even more potent vitamin K reductase inhibitors. Other compounds that have varying degrees of vitamin K antagonistic activity include salicylates and the cephalosporins containing the *N*-methyl-thiotetrazole side chain, such as moxalactam and cefamandole. Because vitamin K can no longer be recycled in the presence of these inhibitors, sufficient doses must be administered to supply this active cofactor for each and every carboxylation step.

AVAILABILITY OF DIFFERENT FORMS OF VITAMIN K

Among the currently marketed vitamin K products, only vitamin K_1 should be used to reverse anticoagulant-induced vitamin K deficiency.

PHARMACOKINETICS AND PHARMACODYNAMICS OF ADMINISTERED VITAMIN K_1

A 10-mg IV dose of vitamin K_1 has a half-life of about 1.7 hours in humans. In maximally brodifacoum-anticoagulated rabbits, IV vitamin K_1 (10 mg/kg) increased prothrombin complex activity (PCA) to approximately 50% by 4 hours and to 100% by 9 hours, after which it declined with a half-life of 6 hours. After oral administration of vitamin K_1, peak concentrations occurred at 3–6 hours and declined with a half-life of about 4 hours. Bioavailability varies significantly between patients and in individual patients with varied doses. Because the pharmacokinetic profile of IM and the pharmacodynamic profile of subcutaneous (SC) vitamin K are highly variable, administration by these routes is not recommended.

ROUTES OF ADMINISTRATION AND ADVERSE EFFECTS

Although vitamin K_1 may be administered orally, subcutaneously, intramuscularly, or intravenously, the oral route is preferred when possible for maintenance therapy. When administered orally, vitamin K_1 is virtually free of adverse effects, except for overcorrection of the INR in the setting of a patient who requires maintenance anticoagulation. The only preparation available for intravenous administration is Aquamephyton, which is associated with rare anaphylactoid reactions, some of which have been fatal. Currently, new liposomal preparations are being developed and may become safer alternatives.

ONSET OF EFFECT

The time necessary for the INR to return to a safe or therapeutic range is quite variable and depends on the rate of absorption of vitamin K_1, the plasma concentration achieved, and the time necessary for the synthesis of activated clotting factors. A decrease in the INR can often occur within several hours, while it may take 8–24 hours to reach target values. Maintenance of a normal INR depends on the half-life of the vitamin K_1, maintenance of an effective plasma concentration, and the half-life of the anticoagulant involved. The IV route is unpredictably faster than the oral route in restoring the INR to a safe range. A comparison of oral versus intravenous vitamin K_1, therapy for excessive anticoagulation without major bleeding, demonstrated that those individuals with INRs 6–10 had similarly improved INRs at 24 hours and that the IV group was more often overcorrected to an INR <2.

DOSING AND ADMINISTRATION

The optimal dosage regimen for vitamin K_1 remains unclear. Reported cases of LAAR poisoning have required as much as 50–250 mg of vitamin K_1 daily for weeks to months, whereas a single dose of 1–10 mg is usually sufficient in patients who are overanticoagulated with warfarin. A reasonable starting approach for a patient who has intentionally overdosed on either warfarin or a LAAR is 25–50 mg of vitamin K_1, orally 3–4 times a day for 1–2 days. Vitamin K_1 is available orally as a 5-mg tablet, requiring the patient to initially consume 5–10 tablets every 6–8 hours. The INR should be monitored and the vitamin K_1 dose adjusted accordingly. Once the INR is <2, a downward titration in the dose of vitamin K_1 can be made on the basis of factor VII analysis. IV administration of vitamin K_1 should be reserved for life-threatening bleeding and serious bleeding at any elevation of INR. Under these circumstances patients may also be supplemented with prothrombin complex concentrate, fresh-frozen plasma, or recombinant factor VIIa. A starting IV dose of 10 mg of vitamin K_1 is reasonable. To minimize the risk of an anaphylactoid reaction, the preparation should be diluted with preservative-free 5% dextrose, 0.9% sodium chloride solution, or 5% dextrose in 0.9% sodium chloride solution, and administered slowly, at a rate not to exceed 1 mg/min in adults. Precautions should be anticipated in the event of an anaphylactoid reaction.

Because the duration of action of vitamin K_1 is short-lived, the dose must be repeated 2–4 times daily. The onset of the effect of vitamin K_1 is not immediate, regardless of the route of administration.

For patients who become overanticoagulated while receiving therapeutic warfarin therapy the dosing and route of vitamin K_1 has been standardized by consensus (Table 57–3).

Protamine

Protamine is a rapidly acting antidote used for reversing the anticoagulant effects of unfractionated heparin (UFH) and for some of the effects of low-molecular-weight heparin (LMWH). The protamines are a group of simple basic cationic proteins found in fish sperm that bind to heparin to form a stable salt. Commercially available protamine sulfate is derived from the sperm of mature testes of salmon and related species.

MECHANISM OF ACTION

Heparin is a large electronegative substance that is rapidly complexed by the electropositive protamine, forming an inactive salt. Heparin is an indirect anticoagulant, requiring a cofactor antithrombin III (AT). Only about one-third of an administered dose binds to AT, and this fraction is responsible for most of its anticoagulant effect. LMWH has a reduced ability to inactivate thrombin because of lesser AT binding, but it inactivates factor Xa almost as well as UFH, allowing equal efficacy. Because protamine has a greater affinity for heparin than AT, the heparin-AT complex dissociates to form a protamine-heparin complex.

ADVERSE EFFECTS, RISK FACTORS, AND SAFETY ISSUES

Although millions of patients have been exposed to protamine during cardiopulmonary bypass surgery, only approximately 100 deaths are associated with the use of protamine. Adverse effects associated with protamine include both rate-related and non–rate-related hypotension, anaphylactic and anaphylactoid reactions, bradycardia, thrombocytopenia, leukopenia, decreased oxygen consumption, acute lung injury, pulmonary hypertension, and anticoagulant effects.

The strong net-positive charge of protamine may be responsible for some of the adverse effects. Additionally, the protamine-heparin complex activates the arachidonic acid pathway and the production of thromboxane is at least partly responsible for some of the hemodynamic changes, including pulmonary hypertension. Multiple other mechanisms have been proposed. A prospective study reported a 0.06% incidence of anaphylactic reactions to protamine in all patients undergoing coronary artery bypass, but a 2% incidence in diabetics using NPH (neutral protamine Hagedorn) insulin.

DOSING IN CARDIOPULMONARY BYPASS

Protamine is most frequently used at the end of cardiopulmonary bypass operations to reverse the effects of heparin. There are many regimens used for protamine dosing, including (a) giving an arbitrary amount of protamine (eg, 0.2 mg/kg); (b) giving protamine in a ratio of 0.6–1.5:1 times the initial heparin dose, resulting in an activated coagulation time (ACT) of about 480 seconds; and (c) giving protamine in a ratio of 0.75–2.1:1 times the total operative heparin dose. Two additional methods of calculating the protamine dose to improve accuracy and avoid excess protamine are proposed. One advocates an initial protamine dose based on ACT, with subsequent doses based

on the ratio of the change in thrombin time to the heparin-neutralized thrombin time. If this ratio is greater than 12 seconds, then 10-mg incremental protamine doses should be administered. The other uses a nomogram based on heparin activity (in mg/kg) versus ACT. Both methods demonstrate efficacy with 2-mg/kg doses of protamine, about one-half of the dose previously used. With these approaches, the ACT responded to protamine within 5 minutes, decreasing in value from 550–700 seconds to a control of 150 seconds.

HEPARIN REBOUND AND REDOSING OF PROTAMINE

A heparin anticoagulant rebound effect is noted after cardiopulmonary bypass and is attributed to the presence of detectable circulating heparin several hours after apparently adequate heparin neutralization with protamine. The incidence of heparin rebound and the need for additional protamine range from 4–42%, depending on the neutralization protocol.

DOSING CONSIDERATIONS

One milligram of protamine will neutralize approximately 100 units (1 mg) of UFH. Unfortunately, there is no proven method for neutralizing LMWH. Protamine neutralizes approximately 60% of the anti-factor Xa activity of LMWH. Because the interaction of protamine and heparin is dependent on the molecular weight (MW) of heparin, the LMWH has reduced protamine binding. Within the first 8 hours following administration, the recommendation for reversal of the antithrombotic effect of LMWH is to administer 1 mg protamine per 100 anti-factor Xa units of LMWH (1 mg of enoxaparin = ~100 anti-factor Xa units). A second dose of 0.5 mg protamine should be administered per 100 anti-factor Xa units if bleeding continues.

Because excessive protamine can act as an anticoagulant, the dose chosen should always be an underestimation of that which is needed. In the case of unintentional overdose, the half-life of heparin should be considered, because half of the administered dose of heparin is eliminated within 60–90 minutes if renal function is normal. Thus in the case of an unintentional overdose without bleeding, the short half-life of heparin and the potential risks of protamine administration usually argue for a conservative approach of patient observation, rather than protamine reversal of anticoagulation. If protamine use is necessary to treat active bleeding, the dose must be administered intravenously over 15 minutes to limit rate-related hypotension.

DOSING IN THE UNKNOWN OVERDOSE SETTING

When faced with a patient believed to have received an overdose of an unknown quantity of heparin, the decision to use protamine should be determined by the presence of a prolonged activated partial thromboplastin time (aPTT) and whether persistent bleeding is present. In each circumstance, the potential risks of protamine use (especially in those who have had a prior life-threatening reaction to protamine, as well as in a diabetic receiving a protamine-containing insulin) and the risks of continued heparin anticoagulation should be evaluated. Because of the routine nature of heparin reversal following cardiopulmonary bypass, consultation with members of the bypass team may be helpful. An empiric dose of protamine may be suggested by the baseline ACT: (a) an ACT of 150 seconds necessitates no protamine; (b) an ACT of 200–300 seconds necessitates 0.6 mg/kg; and (c) an ACT of 300–400 sec-

onds necessitates 1.2 mg/kg of protamine. The ACT should be repeated 5–15 minutes following the protamine dose and in 2–8 hours (to evaluate the potential for heparin rebound) and further dosing should be based on these values.

When the ACT is not available, 25–50 mg of protamine can be administered to an adult and adjusted accordingly. Repeat dosing in several hours may be necessary if heparin rebound occurs. The dose should be administered intravenously slowly over 15 minutes with resuscitative equipment immediately available.

Future interventions for bleeding following heparin may include activated factor VII and adenosine triphosphate. Activated factor VII therapy was recently shown to be successful in treating postoperative bleeding in a patient with renal failure who was given LMWH and aspirin.

AVAILABILITY

Protamine is available either as a parenteral solution ready for injection or as a powder to be reconstituted with 5 mL of sterile or bacteriostatic water for injection. When the vials containing 50 mg of protamine are used, they should be shaken vigorously after the water is added. The final solution of either preparation contains 10 mg/mL of protamine.

58 | Calcium Channel Blockers

Calcium channel blockers (CCBs) were first used experimentally in the 1960s; their use has steadily risen to the point where now they are some of the most frequently prescribed cardiovascular drugs. The combination of compliance-improving sustained-release formulations and potent hemodynamic effects complicates the management of patients poisoned with these drugs. The hallmarks of toxicity include hypotension, from vasodilation and impaired myocardial contractility, and bradydysrhythmias. In severely poisoned patients, no therapeutic intervention is demonstrated to be consistently effective. Management decisions must be made on an individual patient basis with careful assessment of the physiologic response to each treatment.

PHARMACOKINETICS AND TOXICOKINETICS

All CCBs are well absorbed orally and undergo hepatic oxidative metabolism predominantly via CYP3A subgroup of the cytochrome P450 enzyme system. Norverapamil, formed by *N*-demethylation of verapamil, is the only active metabolite, and retains 20% of the activity of the parent compound. Diltiazem is predominantly deacetylated into minimally active deacetyldiltiazem, which is then eliminated via the biliary tract. In overdose, these hepatic enzymes become saturated, reducing the potential control of the first-pass effect and increasing the quantity of active drug absorbed systemically. All CCBs are highly protein bound. Volumes of distribution are large for verapamil (5.5 L/kg) and diltiazem (5.3 L/kg), and somewhat smaller for nifedipine (0.8 L/kg).

Verapamil and diltiazem inhibit CYP3A and also inhibit P-glycoprotein–mediated drug transport into peripheral tissues. This inhibition results in elevated serum concentrations of drugs such as cyclosporine and digoxin, which utilize this transport system. The dihydropyridines do not appear to affect the clearance of other agents via CYP3A or P-glycoprotein–mediated transport.

PATHOPHYSIOLOGY

Calcium plays an integral part in excitation-contraction coupling and myocardial conduction (Fig. 58–1). Initially, Ca^{2+} is driven intracellularly down large concentration and electrical gradients through calcium-specific voltage-sensitive channels. These channels, specifically identified as L-type calcium channels, are located in the plasma membrane of all types of muscle cells. In myocardial cells, this slow Ca^{2+} influx creates the plateau phase (phase 2) of the action potential. The Ca^{2+} then acts as a second messenger by binding to and opening a receptor-operated calcium channel on the sarcoplasmic reticulum which releases Ca^{2+} from the vast stores of the sarcoplasmic reticulum into the cytosol (ie, calcium-induced calcium release). The released calcium causes myocardial contraction. In smooth muscle, the rapid influx of calcium binds calmodulin, and the resulting complex ultimately results in cellular contraction.

All commercially available CCBs exert their physiologic effects by antagonizing L-type voltage-sensitive calcium channels. The differences among their pharmacologic effects are related to a combination of specific receptor affinity and types of antagonism.

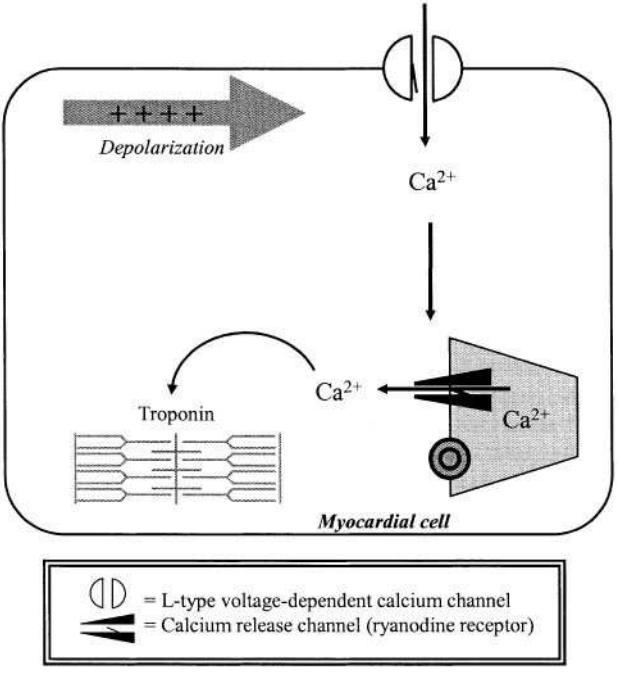


FIG. 58–1. Normal contraction of myocardial cells. The L-type voltage-sensitive calcium channels open to allow calcium ion influx during myocyte depolarization. These calcium ions cause the concentration-dependent release of more calcium ions from the sarcoplasmic reticulum that ultimately produce cardiac contraction.

The CCBs currently available in the United States are classified into three structural groups. Each group binds a slightly different region of the calcium channel and thus has different affinities for the various L-type calcium channels both in the myocardium and the vascular smooth muscle. Verapamil has the most profound inhibitory effects on the sinoatrial (SA) and atrioventricular (AV) nodal tissue, whereas diltiazem has fewer effects and the dihydropyridines have little, if any, direct myocardial effects in therapeutic dosing. As a class, the dihydropyridines have the most potent vasodilatory effects, followed by verapamil, then diltiazem. Consequently, verapamil is the most effective at decreasing heart rate, cardiac output, and blood pressure, whereas nifedipine produces the greatest decrease in systemic vascular resistance. Because nifedipine and all the dihydropyridines have fewer myocardial effects at therapeutic concentrations, the baroreceptor reflex remains intact and a slight increase in heart rate and cardiac output may occur.

CLINICAL MANIFESTATIONS

The life-threatening toxicity of CCBs is manifest largely within the cardiovascular system and is an extension of their therapeutic effects. Myocardial de-

pression and peripheral vasodilation occur, producing hypotension and bradycardia. Myocardial conduction may be impaired, producing AV conduction abnormalities, idioventricular rhythms, and complete heart block. The negative inotropic effects may be so profound, particularly with verapamil, that ventricular contraction may be completely inhibited. Patients initially may present asymptomatically, but deteriorate rapidly into severe cardiogenic shock.

Severe CNS depression is distinctly uncommon, and if respiratory depression or coma is present without severe hypotension, coingestants or other causes of altered mental status must be considered. Gastrointestinal symptoms, such as nausea and vomiting, are also uncommon.

The CCBs with the most significant myocardial effects, verapamil and, to a lesser extent, diltiazem, are associated with more negative inotropic and chronotropic effects. In contrast, nifedipine, because of its limited myocardial binding, may produce tachycardia or a "normal" heart rate. As such, deaths associated with dihydropyridines are relatively uncommon.

Numerous reports document hyperglycemia in patients with severe CCB poisoning. Hyperglycemia is caused by impaired insulin release from the β-islet cells in the pancreas, where release is also dependent on calcium influx via an L-type calcium channel. Acute pulmonary injury is associated with CCB poisoning.

The product formulation (immediate or regular vs. sustained release) affects the onset of symptoms and duration of toxicity. With regular-release formulations, toxicity is often present within 2–3 hours of ingestion. With sustained-release products, however, initial signs or symptoms may be delayed for 6–8 hours, and delays of up to 15 hours are reported.

DIAGNOSTIC TESTING

All patients with a suspected CCB ingestion should be attached to a cardiac monitor and have a 12-lead ECG performed to assess both the heart rate and rhythm, as well the presence of any conduction abnormalities. Routine laboratory testing should be performed. Assays for various CCB serum concentrations are not routinely available and are not used to manage patients after overdose.

MANAGEMENT

Intravenous access and continuous electrocardiographic monitoring should be initiated. A 12-lead ECG should be repeated at least every 1–2 hours for the first several hours. Initial treatment should begin with adequate oxygenation and airway protection (as clinically indicated). If the patient is hypotensive and there is no evidence of congestive heart failure, an initial fluid bolus of 10–20 mL/kg of crystalloid should be given and repeated as needed.

Gastrointestinal decontamination is a critical intervention. Orogastric lavage should be considered for all patients who present early (1–2 hours after ingestion) after large ingestions of non–sustained-release preparations, and for those who are critically ill. It is important to remember that orogastric lavage may increase vagal tone and potentially exacerbate any bradydysrhythmias. Pretreatment with a therapeutic dose of atropine may prevent this. All patients with CCB ingestions should receive 1 g/kg of activated charcoal orally. Multiple doses (0.5 g/kg) of activated charcoal (MDAC) without a cathartic should be administered to all patients with sustained-release pill ingestions or signs of continuing absorption. Whole-bowel irrigation (WBI) with

polyethylene glycol solution (1–2 L/h in adults, up to 500 mL/h in children) should be initiated via nasogastric tube for patients who ingest sustained-release products and may be the most effective way of GI decontamination for ingestions involving these formulations. Dosing should be continued until the rectal effluent is clear.

Pharmacotherapy should focus on maintenance or improvement of both cardiac output and peripheral vascular tone. Although atropine, calcium, insulin, glucagon, isoproterenol, dopamine, epinephrine, norepinephrine, and phosphodiesterase inhibitors have been used with reported success in CCB-poisoned patients, no single therapy has consistently demonstrated total efficacy. A reasonable treatment sequence includes calcium followed by a catecholamine such as norepinephrine, high-dose insulin infusion, glucagon, and a phosphodiesterase inhibitor.

Atropine

Atropine is considered the drug of choice for patients with symptomatic bradycardia. Clinical experience, however, has demonstrated atropine to be largely ineffective in improving heart rate in severe CCB-poisoned patients. Dosing should begin with 0.5–1.0 mg (0.02 mg/kg in children) IV every 2 or 3 minutes up to a maximum dose of 3 mg in all patients with symptomatic bradycardia.

Calcium

Pharmacologically, the use of Ca^{2+} is a logical approach to treat patients with CCB toxicity. Boluses of Ca^{2+} increase the extracellular Ca^{2+} concentration, which increases the transcellular concentration gradient, driving Ca^{2+} intracellularly.

Calcium ion reversed the negative inotropy, impaired conduction, and hypotension in many humans poisoned with CCBs. Ca^{2+} tends to improve blood pressure more than it does the heart rate. Unfortunately, this effect is often short-lived and more severely poisoned patients may not improve significantly with calcium salt administration. Reasonable recommendations for poisoned adults include an initial intravenous bolus of approximately 13–25 mEq of Ca^{2+} (10–20 mL of 10% calcium chloride or 30–60 mL of 10% calcium gluconate) followed by either repeat boluses every 15–20 minutes up to 4 doses or a continuous infusion of 0.5 mEq/kg/h of Ca^{2+} (0.2–0.4 mL/kg/h of 10% calcium chloride or 0.6–1.2 mL/kg/h of 10% calcium gluconate).

If repeat dosing or continuous infusions are used, the serum Ca^{2+} and PO_4^{-3} should be closely monitored to detect if hypercalcemia or hypophosphatemia develop. These concerns are not unfounded and may in fact significantly limit Ca^{2+} therapy. Other adverse effects of intravenous Ca^{2+} include nausea, vomiting, flushing, constipation, confusion, and angina. If there is any suspicion that a cardioactive steroid such as digoxin is involved in an overdose, Ca^{2+} should be avoided until digoxin-specific Fab fragments are administered or such poisoning is excluded (Chap. 62).

Inotropes and Vasopressors

Catecholamines are the next line of therapy in the treatment CCB poisoning. No single agent is consistently effective. This is not surprising given the significant variability in both the CCBs and the patients involved. Mechanistically, however, either stimulation of β_1-adrenergic receptors on the myocardium or of

α_1-adrenergic receptors on the peripheral vascular smooth muscle are the most logical targets, but which one depends on the etiology of the hypotension. Based on their specific pharmacology, norepinephrine appears to be an appropriate initial catecholamine to use in hypotensive CCB-poisoned patients. Its significant β_1-adrenergic activity combats the myocardial depressant effects, while its α_1-adrenergic effects increase peripheral vascular resistance. Dopamine is an indirect-acting vasopressor and may not be adequate in severely stressed patients who may have catecholamine depletion.

Insulin and Glucose

In patients severely poisoned with CCBs, hyperinsulinemia/euglycemia therapy may be beneficial because of its positive inotropic effects. There is growing support for the hypothesis that improved myocardial use of carbohydrates is responsible for clinical improvement. Because of the promising animal evidence, the relative lack of other demonstrably effective therapeutics, the seriousness and potentially fatal nature of CCB poisoning, and the growing clinical successes with this therapy, we recommend hyperinsulinemia/euglycemia therapy early in the clinical course for CCB-poisoned patients. An initial dextrose bolus of 25–50 g (0.5–1 g/kg) should be given, followed by a dextrose infusion at 0.25–0.5 g/kg/h. The initial insulin bolus of 1 unit/kg should be followed by an insulin infusion at a rate of 0.5 units/kg/h, which should be increased if there is no hemodynamic response in 60 minutes. This increase should be done in a stepwise manner with concomitant increases in the dextrose infusion to maintain euglycemic control. Serum glucose and potassium concentrations should be closely monitored throughout therapy, particularly during the first few hours, and should be continued for several hours after discontinuation of the insulin infusion.

Glucagon

Glucagon is an endogenous polypeptide hormone secreted by the pancreatic cells that provides significant inotropic and chronotropic effects. Glucagon is the drug of choice for β-adrenergic antagonist poisoning (Chap. 59). In CCB poisoning, however, because the cellular lesion is "downstream" from adenylate cyclase, glucagon offers no pharmacologic advantage over more traditional β-adrenergic agonists.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors, such as amrinone, milrinone, and enoximone, inhibit the breakdown of cyclic adenosine monophosphate (cAMP) by phosphodiesterase, thereby increasing cAMP levels. These noncatecholamine inotropes increase intracellular calcium and improve inotropy. However, phosphodiesterase inhibitors also cause smooth muscle relaxation, peripheral vasodilation, and often hypotension, which may severely limit their usefulness in many CCB-poisoned patients. They should be used only as a second-line intervention, in combination with another inotrope or vasoconstrictor, and in patients with hemodynamic monitoring.

Adjunctive Hemodynamic Support

Transthoracic or intravenous cardiac pacing may improve heart rate. However, electrical capture may be difficult to attain. In addition, even if electrical

pacing is effective in increasing the heart rate, often blood pressure remains unchanged.

Intraaortic balloon counterpulsation is another invasive supportive option to be considered in cases refractory to pharmacologic therapy, as is cardiopulmonary bypass. These complex therapies are available only at tertiary care facilities.

DISPOSITION

Every patient who manifests any signs or symptoms of toxicity should be admitted to an intensive care setting. Any patient ingesting sustained-release products should be admitted for 24 hours to a monitored setting, even if asymptomatic. All admitted patients should be treated with activated charcoal, and those with a history of sustained-release product ingestion should be treated with WBI. Only patients with a precise history of an "immediate-release" preparation ingestion who have received adequate GI decontamination, who have serial ECGs over 6–8 hours that have remained unchanged, and who are asymptomatic can be "medically cleared."

59 β-Adrenergic Antagonists

There are 18 FDA-approved β-adrenergic antagonists. They are commonly used in the treatment of cardiovascular disease, hypertension, coronary artery disease, and tachydysrhythmias. Additional indications for β-adrenergic antagonists include congestive heart failure, migraine headaches, benign essential tremor, panic attack, stage fright, and hyperthyroidism. Also, ophthalmic preparations containing β-adrenergic antagonists are used in the treatment of glaucoma.

Compared to the other β-adrenergic antagonists, propranolol accounts for a disproportionate number of cases of self-poisoning and deaths. This may be explained by the fact that propranolol is frequently prescribed to patients with diagnoses such as anxiety, stress, and migraine, who may be more prone to suicide attempts. Propranolol is also more lethal because of its lipophilic and membrane-stabilizing properties.

PHARMACOLOGY

The Cardiac Cycle

Normal cardiac electrical activity involves a complex series of ion fluxes that result in myocyte depolarization and repolarization. Electrical activity of the heart is coupled to cell contraction and relaxation, respectively, by increases and decreases in myocyte calcium concentrations. Cardiac electrical and mechanical activity is closely regulated by the autonomic nervous system.

In normal conditions, heart rate is determined by the rate of spontaneous discharge of specialized pacemaker cells that comprise the sinoatrial (SA) node. Spontaneous depolarizations of pacemaker cells are a result of several inward cation channels that are under autonomic control. β-Adrenergic stimulation significantly increases the rate of spontaneous depolarization of pacemaker cells by incompletely understood mechanisms. Depolarization of cells in the SA node spreads to surrounding atrial cells where it triggers the opening of fast sodium channels. This initiates an electric current that spreads along specialized pathways to depolarize the entire heart. This depolarization, referred to as cardiac excitation, is linked to mechanical activity of the heart by the process of electrical–mechanical coupling (also see Chap. 23).

Myocyte Calcium Flow and Contractility

During systole, voltage-sensitive L-type calcium channels on the myocyte membrane open in response to myocyte depolarization and allow extracellular calcium to flow down its concentration gradient into the myocyte. This local increase in intracellular calcium concentrations triggers the opening of an array of sarcoplasmic reticulum (SR) calcium release channels, resulting in a large release of calcium from the SR, a phenomenon known as calcium-induced calcium release. The result is myocyte contraction, which, in turn, is proportional to myocyte calcium concentrations.

β-Adrenergic Receptors and the Heart

The most prevalent subtype of β-adrenergic receptor in the heart is the β_1-subtype receptor, but there are cardiac β_2- and β_3-adrenergic receptors as well.

β_1-Adrenergic receptors increase inotropy and chronotropy that involves cyclic adenosine monophosphate (cAMP) generation via adenyl cyclase.

Noncardiac Effects of β-Adrenergic Receptor Activation

β_2-Adrenergic receptors mediate smooth muscle relaxation in several organs. Relaxation of arteriolar smooth muscle by β_2-adrenergic stimulation reduces peripheral vascular resistance and decreases blood pressure. This counteracts α-adrenergic–mediated arteriolar constriction. In the lungs, β_2-adrenergic receptors mediate bronchodilation. Third-trimester-uterine tone and contractions are inhibited by β_2-adrenergic agonists, and gut motility is decreased by both β_1- and β_2-adrenergic stimulation.

Action of β-Adrenergic Antagonists

β-Adrenergic antagonists competitively antagonize the effects of catecholamines at the β-adrenergic receptor and blunt the chronotropic and inotropic response to catecholamines. Bradycardia and hypotension may be severe in patients with underlying cardiac conduction defects, and in those who take calcium channel blockers or other medications that impair cardiac conduction and contraction. Even in those patients without underlying heart disease, the effects of β-adrenergic antagonists on the SR and intracellular calcium handling may produce hypotension and bradycardia.

Patients with reactive airways disease may suffer severe bronchospasm after using β-adrenergic antagonists as a result of loss of β_2-adrenergic–mediated bronchodilation. Catecholamines inhibit mast cell degranulation through a β_2-adrenergic mechanism. Interference with this may predispose to life-threatening effects following anaphylactic reactions in atopic individuals.

β-Adrenergic antagonists prevent catecholamine-mediated potassium uptake at skeletal muscle. This may cause slight elevations in serum potassium, especially after exercise. Although β_2-adrenergic stimulation augments insulin release, β-adrenergic antagonists seldom lower insulin concentrations and β-adrenergic antagonists may actually cause hypoglycemia by interference with glycogenolysis and gluconeogenesis.

PHARMACOKINETICS

The highly lipid-soluble drugs cross lipid membranes rapidly and concentrate in adipose tissue (Table 59–1). These properties allow rapid entry into the CNS and add the requirement for biotransformation prior to renal elimination. Highly water-soluble drugs, in contrast, cross lipid membranes slowly and distribute in total-body water. These drugs are generally slowly absorbed, poorly protein bound, renally eliminated, and slow to enter the CNS. They tend to accumulate in patients with renal failure and generally have less CNS toxicity. Atenolol is the most water-soluble β-adrenergic antagonist.

β_1 Selectivity

β_1-Selective drugs may avoid some of the adverse effects of the nonselective drugs. The β_1-adrenergic selectivity is incomplete and adverse reactions secondary to β_2-adrenergic antagonism may occur with even therapeutic dosage.

TABLE 59–1. Pharmacologic Properties of the β-Adrenergic Antagonists[a]

	Adrenergic Blocking Activity	Partial Agonist Activity (ISA)	Membrane Stabilizing Activity	Vasodilating Property	Lipid Solubility	Half-Life (h)	Metabolism
Acebutolol	β_1	Yes	Yes	No	Low	2–4	Hepatic/renal
Atenolol	β_1	No	No	No	Low	5–9	Renal
Betaxolol[b]	β_1	No	Yes	Yes (calcium channel blockade)	Low	14–22	Hepatic/renal
Bisoprolol	β_1	No	No	No	Low	9–12	Hepatic/renal
Bucindolol	β_1, β_2	β_2 agonism		Yes (β_2 agonism)	Moderate	8 ± 4.5	Hepatic
Carteolol[b]	β_1, β_2	Yes	No	Yes (β_2 agonism and nitric oxide mediated)	Low	5–6	Renal
Carvedilol	$\alpha_1, \beta_1, \beta_2$	No		Yes (α_1 blockade)	Moderate	6–10	Hepatic
Celiprolol	α_2, β_1	β_2 agonism		Yes (β_2 agonism)	Low	5	Hepatic
Esmolol	β_1	No	No	No	Low	~8 min	RBC esterases
Labetalol[b]	$\alpha_1, \beta_1, \beta_2$	No	Low	Yes (α_1 antagonism)	Moderate	4–8	Hepatic
Levobunolol	β_1, β_2	No	No	No	NA	6	NA
Metipranolol[b]	β_1, β_2	No	No	No	NA	3–4	NA
Metoprolol[c]	β_1	No	Low	No	Moderate	3–4	Hepatic
Nadolol	β_1, β_2	No	No	No	Low	10–24	Renal
Nebivolol	β_1	No		Yes (nitric oxide mediated?)	Moderate	8–32	Hepatic
Oxprenolol	β_1, β_2	Yes	Yes	No	Moderate	1–3	Hepatic
Penbutolol	β_1, β_2	Yes	No	No	High	5	Hepatic/renal
Pindolol	β_1, β_2	Yes	Low	No	Moderate	3–4	Hepatic/renal
Propranolol[c]	β_1, β_2	No	Yes	No	High	3–5	Hepatic
Sotalol	β_1, β_2	No	No	No	Low	9–12	Renal
Timolol[b]	β_1, β_2	No	No	No	Moderate	3–5	Hepatic/renal

ISA = intrinsic sympathomimetic activity.
[a]Agents in italics are *not* FDA approved. The notation *"NA"* indicates that information is not available.
[b]Ophthalmic preparation.
[c]Long-acting formulation available.

Membrane-Stabilizing Effects (Acebutolol, Betaxolol, Oxprenolol, Propranolol)

β-Adrenergic antagonists that inhibit fast sodium channels are said to possess membrane-stabilizing activity (also known as type I antidysrhythmic activity). After overdose, QRS complex duration prolongation and hypotension, both manifestations of sodium channel blockade, may occur.

Intrinsic Sympathomimetic Activity (Acebutolol, Oxprenolol, Penbutolol, Pindolol)

These drugs act as partial agonists at β-adrenergic receptors and are said to have intrinsic sympathomimetic activity (ISA). These drugs may avoid the severe decrease in resting heart rate that occurs with β-adrenergic antagonism in susceptible patients.

Potassium Channel Blockade (Sotalol)

Sotalol is a nonselective β-adrenergic antagonist that is unique because of its ability to block the delayed rectifier potassium current (I_{Kr}) responsible for repolarization. This prolongs the action potential duration and is manifested on the electrocardiogram by a prolonged QTc. The prolonged QTc predisposes to torsades de pointes and ventricular dysrhythmias may complicate even the therapeutic use of sotalol.

Vasodilation (Betaxolol, Carvedilol, Labetalol)

Labetalol and the newer "third-generation" β-adrenergic antagonists are also vasodilators. Labetalol and carvedilol are nonselective β-adrenergic antagonists that also possess α-adrenergic antagonist activity. Nebivolol and carteolol are selective β_1-adrenergic antagonists that cause vasodilation by release of nitric oxide. Bucindolol, carteolol, and celiprolol are β_1-adrenergic antagonists that vasodilate because they are agonists at the β_2-adrenergic receptors. Betaxolol vasodilates because of its calcium channel blocking properties.

β-Adrenergic antagonists are contraindicated in situations of catecholamine excess such as pheochromocytoma and cocaine toxicity. In these conditions, β_2-adrenergic–mediated vasodilation is essential to counteract α-adrenergic–mediated vasoconstriction. β-Adrenergic antagonist administration would result in an "unopposed" α-adrenergic effect, causing dangerous increases in peripheral vascular resistance (Chap. 74). Even drugs with combined α- and β-adrenergic antagonist properties can cause this problem.

Ophthalmic Preparations

Therapeutic use of ophthalmic solutions containing β-adrenergic antagonists may cause adverse effects such as bradycardia, high-grade atrioventricular (AV) block, heart failure, bronchospasm, and depression.

PATHOPHYSIOLOGY

Most of the toxicity of β-adrenergic antagonists is a result of their ability to competitively antagonize the action of catecholamines at cardiac β-adrenergic receptors. The peripheral effects of β-adrenergic antagonism are less prominent in overdose. A membrane-depressant effect may contribute to the cardiac-depressant effects of propranolol, but this cannot account for the car-

diac depressant effects of most of the other β-adrenergic antagonists. β-Adrenergic antagonists also cause myocardial depression, at least in part, by an action independent of either catecholamine antagonism or membrane-depressant activity.

CLINICAL MANIFESTATIONS

β-Adrenergic antagonist overdose in submassive amounts in healthy people is generally quite benign. When it occurs, toxicity generally occurs early following ingestion. Propranolol overdose, in particular, may be complicated by the rapid development of seizures, coma, and dysrhythmias. β-Adrenergic antagonists also cause respiratory depression, which is likely centrally mediated.

β-Adrenergic antagonists severely impair the heart's ability to respond to peripheral vasodilation, bradycardia, and decreased contractility caused by other toxins. Consequently, even relatively benign vasoactive xenobiotics can cause catastrophic toxicity when coingested with β-adrenergic antagonists. β-Adrenergic antagonist overdose is most likely to cause symptoms in persons with congestive heart failure, sick sinus syndrome, or impaired AV conduction who rely on sympathetic stimulation to maintain heart rate or cardiac output.

Patients with symptomatic β-adrenergic antagonist overdose will most often be hypotensive and bradycardic. Prolonged QRS and QTc intervals may occur, and severe poisonings may result in asystole. Congestive heart failure often complicates β-adrenergic antagonist overdose. Delirium, coma, and seizures occur most commonly in the setting of severe hypotension but may also occur with normal blood pressure, especially with exposure to the more lipophilic drugs. Hypoglycemia may complicate β-adrenergic antagonist poisoning in children but is uncommon in acutely poisoned adults. Bronchospasm is relatively uncommon following β-adrenergic antagonist overdose and appears to occur only in susceptible patients. Note that in overdose, cardioselectivity is largely lost.

Membrane-Stabilizing Effects (Acebutolol, Betaxolol, Oxprenolol, Propranolol)

Propranolol possesses the most membrane-stabilizing activity of this class. Propranolol poisoning is characterized by coma, seizures, hypotension, bradycardia, impaired atrioventricular conduction, widened QRS interval, and ventricular tachydysrhythmias.

Lipid Solubility

In overdose, the more lipophilic β-adrenergic antagonists may cause delirium, coma, and seizures even in the absence of hypotension. Atenolol, the least lipid soluble of the β-adrenergic antagonists, appears to be one of the safer β-adrenergic antagonists when taken in overdose, although cardiovascular death may occur.

Intrinsic Sympathomimetic Activity

There is little experience with overdose, but ISA theoretically makes these drugs less problematic than the other β-adrenergic antagonists. Sympathetic stimulation with mild tachycardia or hypertension often predominates in pindolol overdose, and this drug appears to be relatively safe in overdose.

Potassium Channel Blockade

Ventricular dysrhythmias, including multifocal ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation, should be expected. Sotalol overdose may also be complicated by hypotension, bradycardia, and asystole, and the onset may be delayed and the effects prolonged.

Vasodilation

The α_1-adrenergic antagonism of labetalol and carvedilol theoretically acts in synergy with β-adrenergic antagonism to increase toxicity. Conversely, the low membrane-stabilizing effect of these drugs may make them relatively safe in overdose. Overdose with labetalol appears to be similar clinically to that of other β-adrenergic antagonists, with hypotension and bradycardia the prominent features. Experience with carvedilol overdose is extremely limited.

Other Preparations

Although there is very little published experience with overdoses of the sustained-release β-adrenergic antagonists, it is reasonable to expect that overdose with these drugs will result in both a delayed onset and a prolonged duration of toxicity. Patients who take mixed overdoses with calcium channel antagonists and β-adrenergic antagonists are difficult to manage because of synergistic toxicity.

DIAGNOSTIC TESTING

All patients with an intentional overdose of a β-adrenergic antagonist should have a 12-lead electrocardiogram and continuous cardiac monitoring. Serum glucose should be measured regardless of mental status as β-adrenergic antagonists can cause hypoglycemia. A chest radiograph and measurement of oxygen saturation should be obtained if the patient appears to be at risk for congestive heart failure. For patients with bradycardia of uncertain etiology, measurement of potassium, renal function, cardiac enzymes, and digoxin concentrations may prove helpful. Serum concentrations of β-adrenergic antagonists are not readily available for routine clinical use, but may prove helpful in making a retrospective diagnosis in selected cases.

MANAGEMENT

The initial management of the critically ill patient who ingests β-adrenergic antagonists is similar to that for other acutely ill patients and includes symptomatic and supportive care. The initial treatment of bradycardia and hypotension consists of atropine and fluids. Consideration for GI decontamination is warranted for all persons who have ingested significant amounts of a β-adrenergic antagonist. Orogastric lavage is recommended for patients with symptoms, such as seizures, significant hypotension, or bradycardia, if the drug is still expected to be in the stomach. We recommend activated charcoal alone for persons with minor symptoms following an overdose with one of the more water-soluble β-adrenergic antagonists who present later than 1 hour following ingestion. Whole-bowel irrigation with polyethylene glycol should be considered in patients who have ingested sustained-release preparations (see Antidotes in Brief: Whole-Bowel Irrigation).

Specific Management

Patients who fail to respond to atropine and fluids require management with inotropic agents. We recommend glucagon followed by calcium, high-dose insulin, a catecholamine pressor, and if this fails, phosphodiesterase inhibitors. In the critically ill patient there may not be enough time for this approach, and multiple treatments may be started simultaneously. Advanced hemodynamic monitoring, when available, is advisable to guide therapy for all patients receiving catecholamine pressors or phosphodiesterase inhibitors.

Glucagon

Humans have cardiac glucagon receptors that, like β-adrenergic receptors, are coupled to G_s proteins. Glucagon binding increases adenyl cyclase activity independent of β-adrenergic receptor binding. Glucagon's inotropic effect is enhanced by its ability to inhibit phosphodiesterase, preventing cAMP breakdown.

The initial adult dose of glucagon for β-adrenergic antagonist toxicity is 3–5 mg given slowly over 1–2 minutes. The initial pediatric dose is 50 μg/kg. If there is no response to the initial dose, higher doses up to a total of 10 mg may be used. Once a response occurs, a glucagon infusion is started. Most authors recommend using an infusion of 2–5 mg/h, although many authorities recommend glucagon infusions as high as 10 mg/h. We suggest that the glucagon infusion be started at the "response dose" per hour. Even when a full dose of glucagon fails to restore blood pressure and heart rate and the diagnosis of β-adrenergic antagonist toxicity is probable, we still recommend starting an infusion of glucagon at 10 mg/h as glucagon will have synergistic effects with subsequent agents. Glucagon may cause vomiting with the risk of aspiration (see Antidotes in Brief: Glucagon).

Calcium

Calcium salts effectively treat hypotension from calcium channel blocker overdose and are also effective in restoring blood pressure, but not heart rate in animal models of β-adrenergic antagonist toxicity. Reasonable recommendations for poisoned adults include an initial intravenous bolus of approximately 13–25 mEq of Ca^{2+} (10–20 mL of 10% calcium chloride or 30–60 mL of 10% calcium gluconate) followed by either repeat boluses every 15–20 minutes up to 4 doses or a continuous infusion of 0.5 mEq/kg/h of Ca^{2+} (0.2–0.4 mL/kg/h of 10% calcium chloride or 0.6–1.2 mL/kg/h of 10% calcium gluconate).

If repeat dosing or continuous infusions are used, the serum Ca^{2+} and PO_4^{-3} should be closely monitored to detect if hypercalcemia or hypophosphatemia develop. These concerns are not unfounded and may in fact significantly limit Ca^{2+} therapy. Other adverse effects of intravenous Ca^{2+} include nausea, vomiting, flushing, constipation, confusion, and angina. If there is any suspicion that a cardioactive steroid such as digoxin is involved in an overdose, Ca^{2+} should be avoided until digoxin-specific Fab fragments are administered or such poisoning excluded (Chap. 62).

Insulin and Glucose

High-dose insulin is effective in animal models of verapamil toxicity and myocardial infarction and is routinely used for patients with severe calcium channel blocker poisoning (Chap. 58). High-dose insulin and glucose therapy was also effective in human cases of combined calcium channel blocker and

β-adrenergic antagonist toxicity and experimental models of β-adrenergic antagonist toxicity. An initial dextrose bolus of 25–50 g (0.5–1 g/kg) should be given, followed by a dextrose infusion at 0.25–0.5 g/kg/h. The initial insulin bolus of 1 unit/kg should be followed by an insulin infusion of 0.5 units/kg/h, which should be increased if there is no hemodynamic response in 60 minutes. This increase should be done in a stepwise manner with concomitant increases in the dextrose infusion to maintain euglycemic control. Serum glucose and potassium concentrations should be closely monitored throughout therapy, particularly during the first few hours, and should be continued for several hours after discontinuation of the insulin infusion.

Catecholamines

Patients who do not respond to the preceding therapies usually require a catecholamine infusion. The choice of catecholamine is somewhat controversial as each has theoretical benefits and liabilities. Because of the potential problems, we recommend that catecholamine use be guided by hemodynamic monitoring using invasive or noninvasive measurements (eg, bioimpedance techniques or echocardiographic monitoring) of cardiac performance. Regardless of which drug is chosen, catecholamine infusions should be started at the usual rates and then increased rapidly until a clinical effect is obtained. If advanced monitoring is impossible and the diagnosis of β-adrenergic antagonist overdose is fairly certain, it is reasonable to begin an isoproterenol or epinephrine infusion with careful monitoring of the patient's blood pressure and clinical status.

Phosphodiesterase Inhibitors

The phosphodiesterase inhibitors (PDIs) amrinone, milrinone, and enoximone are theoretically beneficial in β-adrenergic antagonist overdose because they increase inotropy in the presence of β-adrenergic antagonism. Therapy with PDIs is often limited by hypotension secondary to peripheral vasodilation and they should generally only be considered for patients who have arterial and pulmonary artery pressure monitoring.

Ventricular Pacing

Ventricular pacing is not a particularly useful intervention in patients with β-adrenergic antagonist toxicity but it will increase the heart rate in some patients. Unfortunately, there frequently will be failure to capture or pacing may increase the heart rate with no increase in cardiac output or blood pressure.

Extracorporeal Removal

Extracorporeal removal is ineffective for the lipid-soluble β-adrenergic antagonists because of their large volumes of distribution. Hemodialysis may remove water-soluble renally eliminated β-adrenergic antagonists such as atenolol and acebutolol. However, hemodialysis is technically difficult in these patients because of hypotension and bradycardia.

Mechanical Life Support

It is important to remember that the patient with severe hypotension from an acute overdose will typically recover without sequelae if ventilation and circulation can be maintained until the xenobiotic is eliminated. When the preceding medical treatment fails, it is appropriate to consider the use of an intraaortic balloon pump or extracorporeal circulation.

Special Circumstances

Sotalol

Sotalol toxicity may result in a prolonged QTc and ventricular dysrhythmias, including torsades de pointes, in addition to bradycardia and hypotension. Sotalol-induced bradycardia and hypotension should be managed as with other β-adrenergic antagonists. However, extreme care must be used to avoid hypokalemia, which is common with both β-adrenergic agonist and insulin infusions. Specific management of patients with sotalol overdose includes correction of hypocalcemia and hypomagnesemia to avoid precipitating torsades de pointes.

Peripheral Vasodilating Effect

Treatment is similar to that for patients who ingest other β-adrenergic antagonists, although a greater emphasis on intravascular volume loading may be necessary. Vasopressors use should be guided by clinical findings. If vasodilation is a prominent feature, pressors with α-adrenergic agonist properties (eg, norepinephrine or phenylephrine) may be best suited.

Membrane-Stabilizing Effects

It might be expected that hypertonic sodium bicarbonate would be beneficial in treating the ventricular dysrhythmias that occur with these drugs. Unfortunately, there is limited experience with the use of bicarbonate in this situation, and the experimental data are mixed. Because bicarbonate is a relatively safe and simple intervention, we recommend that it be used in addition to standard therapy for β-adrenergic antagonist–poisoned patients with QRS widening, ventricular dysrhythmias, or severe hypotension.

Observation

All patients who have bradycardia, hypotension, abnormal ECGs, or CNS toxicity following a β-adrenergic antagonist overdose should be observed in an intensive care setting until these findings resolve. Toxicity from regular-release β-adrenergic antagonist poisoning, other than with sotalol, almost always occurs within the first 6 hours. Therefore patients without any findings of toxicity following an overdose of a regular-release β-adrenergic antagonist, other than sotalol, may be discharged from medical care after an observation time of 6–8 hours if they remain asymptomatic with normal vital signs and a normal electrocardiogram, and have had GI decontamination with at least activated charcoal. Because ingestion of extended-release preparations may cause delayed toxicity, these patients should be observed for 24 hours in an intensive care unit. We also recommend 24 hours of observation for all patients with sotalol overdose because of the risk of delayed dysrhythmias.

Glucagon

Glucagon is a polypeptide counterregulatory hormone with a molecular weight of 3500 daltons, secreted by the α cells of the pancreas. Previously animal derived, the currently FDA-approved form has been synthesized by recombinant DNA technology since 1998. Its traditional role is to reverse life-threatening hypoglycemia in diabetic patients who are unable to ingest dextrose in the outpatient setting. In medical toxicology, however, glucagon is used in the management of β-adrenergic antagonist and calcium channel blocker overdoses.

MECHANISM OF ACTION

Glucagon receptors are identified in the human heart and brain and resemble those on the pancreas. The binding of glucagon to its receptor stimulates adenylate cyclase to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). This increases inotropy and chronotropy in the heart. Stimulation of glucagon receptors in the liver and adipose tissue increases glycogenolysis, gluconeogenesis, and ketogenesis. Other properties of glucagon include relaxation of smooth muscle in the lower esophageal sphincter, stomach, small and large intestines, common bile duct, and ureters.

PHARMACOKINETICS AND PHARMACODYNAMICS

In human volunteers, after a single IV bolus, the effects of glucagon on the heart begin within 1–3 minutes, are maximal within 5–7 minutes, and persist for 10–15 minutes. The time to maximal glucose concentration is 5–20 minutes, with a duration of action of 60–90 minutes. Smooth muscle relaxation begins within 1 minute and lasts 10–20 minutes. Tachyphylaxis or desensitization may occur with continual dosing.

CARDIOVASCULAR EFFECTS

The inotropic action of glucagon appears to be related to an increase in cardiac cAMP concentrations. Thus the positive inotropic and chronotropic actions of glucagon are very similar to those of the β-adrenergic agonists except that they are not blocked by β-adrenergic antagonists. Glucagon is not dysrhythmogenic in patients with severe chronic congestive heart failure or myocardial infarction–related acute congestive heart failure, and in postoperative patients with myocardial depression.

Evidence now suggests an additional mechanism of action for glucagon independent of cAMP and dependent on arachidonic acid. Cardiac tissue metabolizes glucagon, liberating mini-glucagon, an apparently active smaller terminal fragment. Mini-glucagon stimulates phospholipase A_2, releasing arachidonic acid. Arachidonic acid then acts to increase cardiac contractility through an effect on calcium.

VOLUNTEER STUDIES

In patients with heart failure, glucagon increases the force of contraction as measured by maximum dP/dT, heart rate, cardiac index, blood pressure, and

stroke work. There is no change in systemic vascular resistance, left-ventricular end-diastolic pressure (LVEDP), or stroke index.

ROLE IN OVERDOSES WITH β-ADRENERGIC ANTAGONISTS

Overdoses with β-adrenergic antagonists are particularly dangerous and are manifested by hypotension, bradycardia, prolonged atrioventricular conduction times, depressed cardiac output, cardiac failure, and death. Management is often complicated and many agents are used with variable success. Glucagon increases contractility, restores the sinus node function after sinus node arrest, increases atrioventricular (AV) conduction time, and improves survival. Glucagon has successfully reversed bradydysrhythmias and hypotension in patients previously unresponsive to multiple other drugs, and should be administered early in the management of patients with severe overdoses. By increasing myocardial cAMP concentrations independent of the β receptor, glucagon is able to increase the inotropic and the chronotropic activity of the heart.

ROLE IN CALCIUM CHANNEL BLOCKER OVERDOSE

Calcium channel blocker overdoses produce a constellation of clinical findings similar to those recognized with β-adrenergic antagonist overdoses, including hypotension, bradycardia, heart block, and myocardial depression. Glucagon reverses the myocardial depression produced by nifedipine, diltiazem, and verapamil.

REVERSAL OF HYPOGLYCEMIA

Glucagon was formerly proposed to be part of the initial treatment for all comatose patients. Glucagon stimulates the breakdown of glycogen in the liver to glucose. The theoretical rationale for this approach is only partially sound: hypoglycemic patients may present in coma or with an altered mental status and hypoglycemia can be present concomitantly with a drug overdose. Immediately restoring the patient's blood glucose concentration may be lifesaving. Glucagon, however, requires time to act and may be ineffective in a patient with depleted glycogen stores. Patients with type 2 diabetes are also more likely to respond than are patients with type 1 diabetes. Intravenous dextrose is preferred.

ADVERSE EFFECTS AND SAFETY ISSUES

Side effects associated with glucagon include dose-dependent nausea, vomiting, hyperglycemia, hypoglycemia, hypokalemia, and relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon, and, rarely, urticaria, respiratory distress, and hypotension.

DOSING

An initial IV bolus of 50 μg/kg infused over 1–2 minutes is recommended (3–5 mg in a 70-kg person). Higher doses may be necessary if the initial bolus is ineffective, and up to 10 mg may be used in an adult. In many cases, the bolus dose is followed by a continuous infusion of 2–5 mg/h (up to 10 mg/h) in 5% dextrose in water, which can then be tapered as the patient improves. Since tachyphylaxis occurs with continuous infusion, repeated bolus doses may be necessary.

AVAILABILITY

Glucagon (rDNA origin) by Eli Lilly and Company is available as a 1-mg (1 unit) lyophilized powder for injection with an accompanying 1 mL of diluent in a disposable syringe. The diluent contains 12 mg/mL of glycerin water for injection, and hydrochloric acid, if needed for pH adjustment. Glucagon (rDNA origin) as GlucaGen by Novo Nordisk A/S is available as a 1-mg (1 unit) lyophilized powder for injection. It should be reconstituted with 1 mL of sterile water for injection. Concentrations greater than 1 mg/1 mL should not be used.

60 | Other Antihypertensives

As our understanding of the medical complications of chronic hypertension has grown and the evidence supporting that its treatment improves long-term morbidity and mortality, an increasing number of antihypertensive drugs have become available (Table 60–1). Although overdoses involving these drugs are rarely reported, either because of limited use (eg, reserpine, trimethaphan, and methyldopa) or limited toxicity (eg, diuretics and angiotensin II receptor antagonists), poisoning does occur. Most of the adverse effects and toxicity in overdose are exaggerated pharmacologic effects.

CLONIDINE AND OTHER CENTRALLY ACTING ANTIHYPERTENSIVES

Clonidine is an imidazoline compound that has potent α_2-adrenergic agonist effects. Clonidine is the best understood and the most commonly used of all the centrally acting antihypertensives, a group that includes methyldopa, guanfacine, and guanabenz. Although these drugs differ chemically and structurally, they all decrease blood pressure in a similar manner—by reducing the sympathetic outflow from the CNS. Other imidazolines—oxymetazoline and tetrahydrozoline—which are used as ocular and nasal topical vasoconstrictors and decongestants, produce similar systemic effects when ingested (Chap. 50).

Although the use of clonidine as an antihypertensive has decreased, it has found a wide variety of new applications including attention deficit hyperactivity disorder (ADHD), peripheral nerve and spinal anesthesia, and in the management of substance withdrawal.

Pharmacology and Pharmacokinetics

Clonidine is well absorbed from the GI tract (approximately 75%) with an onset of action within 30–60 minutes. The plasma concentration peaks at 2–3 hours and lasts as long as 8 hours. The majority of clonidine is eliminated unchanged via the kidneys. The patch formulation of clonidine allows slow, continuous delivery of drug over a prolonged period of time, typically 1 week. Each patch contains significantly more drug than is typically delivered during the prescribed duration of use, and much of the drug remains in the patch after discontinuing its use. Both of these issues raise concern for overdose.

Guanabenz and guanfacine are structurally and pharmacologically very similar. They are well absorbed orally, achieving peak concentrations within 3–5 hours. Guanabenz is metabolized predominantly in the liver and undergoes extensive first-pass effect, whereas guanfacine is eliminated equally by the liver and kidney. Neither drug has significant active metabolites.

Methyldopa is a prodrug that requires conversion to α-methylnorepinephrine for activity. Approximately 50% of an oral dose of methyldopa is absorbed and peak serum concentrations are achieved in 2–3 hours. It is eliminated in the urine, both as parent compound and after hepatic sulfation.

Pathophysiology

Clonidine and the other centrally acting antihypertensives exert their hypotensive effects primarily via stimulation of presynaptic α_2-adrenergic re-

TABLE 60–1. Classification of Antihypertensives Available in the United States

β-Adrenergic antagonists (Chap. 59)
Calcium channel blockers (Chap. 58)
Sympatholytics
Central α_2-adrenergic agonists
Clonidine, guanabenz, guanfacine, methyldopa
Ganglionic blockers
Trimethaphan
Peripheral adrenergic neuron antagonists
Guanethidine, guanadrel, metyrosine, reserpine
Peripheral α_1-adrenergic antagonists
Prazosin, terazosin, doxazosin
Diuretics
Thiazides
Bendroflumethiazide, chlorthalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, trichlormethiazide
Loop diuretics
Bumetanide, ethacrynic acid, furosemide, torsemide
Potassium sparing
Amiloride, eplerenone, spironolactone, triamterene
Vasodilators
Hydralazine, minoxidil, diazoxide, nitroprusside
Angiotensin-converting enzyme inhibitors
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
Angiotensin II receptor blockers
Candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan

ceptors in the brain. This results in decreased sympathetic outflow from the CNS and reduces heart rate, vascular tone, and, ultimately, arterial blood pressure. In large doses, peripheral postsynaptic α_2-adrenergic stimulation can occur. Other imidazolines, including oxymetazoline and tetrahydrozoline, produce similar pharmacologic effects when ingested.

Direct stimulation of imidazoline-specific binding sites in the brain lowers blood pressure independent of central α_2-adrenergic effects. Therefore, although their precise physiologic relationship has not been clearly elucidated, evidence supports the concept that both imidazoline and α_2-adrenergic receptors modulate the ability of clonidine, and presumably other centrally acting antihypertensives, to inhibit central norepinephrine release and the cardiovascular effects.

Clinical Manifestations

Although the majority of the published cases involve clonidine, the signs and symptoms of poisoning with any centrally acting antihypertensive are similar. The CNS and cardiovascular toxicity reflect an exaggeration of their pharmacologic action. Common signs include CNS depression, bradycardia, hypotension, and occasionally hypothermia. Most patients who ingest clonidine and the other similarly acting drugs will manifest symptoms rapidly, typically within 30–90 minutes. The exception may be methyldopa, which requires metabolism to be activated, possibly delaying toxicity for hours.

CNS depression is the most frequent clinical finding and can vary from mild lethargy to coma. Respirations may be slow and shallow with intermittent deep sighing breaths. The CNS and respiratory depression typically resolves over 12–36 hours. Other manifestations of this CNS depression include hypotonia, hyporeflexia, and irritability.

Sinus bradycardia, usually associated with hypotension, is common following overdose. Other conduction abnormalities including first-degree heart block, Wenckebach block, 2:1 atrioventricular block, and complete heart block are described both in overdose and after therapeutic dosing.

Paradoxically, severe hypertension may be noted early in dosing, particularly during intravenous administration, or in massive overdoses. This is the result of peripheral α_2-adrenergic agonism. Typically, this hypertensive effect is short-lived, as the central sympatholytic effects become predominant and hypotension ensues. However, in patients with massive ingestions, hypertension may be protracted and require pharmacologic intervention.

Hypothermia is associated with overdoses involving centrally acting antihypertensives, likely a result of α-adrenergic effects within the thermoregulatory center.

Fatalities are rare. This may be because these drugs effectively block all sympathetic outflow from the CNS and this physiologic effect is not essential for life. The CNS depression resulting in hypoventilation, hypoxia, and poor airway protection may be more pronounced in fatalities.

Diagnostic Testing

Because clonidine and other centrally acting antihypertensives are not routinely included in serum or urine toxicologic assays, management decisions should be based on clinical parameters. No electrolyte or hematologic abnormalities are associated with this exposure. Because of the potential for bradydysrhythmias and hypoventilation, a 12-lead ECG and continuous cardiac and pulse oximetry monitoring are strongly recommended during the assessment.

Management

Appropriate therapy begins with particular focus on the patient's respiratory and hemodynamic status. Administration of activated charcoal is the primary mode of GI decontamination in most ingestions, if considered safe. Induction of emesis is contraindicated and orogastric lavage is of limited utility. Patients often present following the onset of symptoms rather than immediately after ingestion, and patients respond well to supportive care. In cases involving clonidine patch ingestions, whole-bowel irrigation may be an effective intervention.

All patients with CNS depression should be evaluated for hypoxia and hypoglycemia. Respiratory compromise, including apnea, often responds well to simple auditory or tactile stimulation. Several clonidine-poisoned patients have had significant arousal after naloxone administration, as well as an increase in respiratory effort, heart rate, and blood pressure.

Isolated hypotension should initially be treated with intravenous boluses of crystalloid. Bradycardia is typically mild and usually does not require any therapy if adequate peripheral perfusion exists. If the bradycardia is severe, however, standard doses of atropine are often effective. Dopamine may be beneficial in patients with refractory bradycardia or hypotension.

The use of α-adrenergic antagonists, such as tolazoline and yohimbine, as specific antidotes for patients with α-adrenergic agonist overdoses is controversial and cannot be recommended in the primary management strategy.

The early-onset hypertension is typically transient, and therapy should be cautiously undertaken with this expectation. If hypertension is severe or prolonged, then treatment with an infusion of sodium nitroprusside is appropriate.

Withdrawal

Abrupt cessation of central antihypertensive therapy may result in withdrawal, which is characterized by excessive sympathetic activity. Symptoms include agitation, insomnia, tremor, palpitations, and hypertension that begins between 16 and 48 hours after cessation of therapy. Ventricular tachycardia and myocardial infarction may occur. Although this phenomenon is associated with all centrally acting α_2-agonists, it appears to be most prominent in the shorter-acting agents such as clonidine and guanabenz. Reasonable treatment strategies include administering clonidine, via either the oral or intravenous route, followed by a closely monitored tapering of the dosing over several weeks, or use of benzodiazepines.

OTHER SYMPATHOLYTIC ANTIHYPERTENSIVES

Several other agents exert their antihypertensive effect by decreasing the effects of the sympathetic nervous system. Often termed *sympatholytics*, they can be classified as ganglionic blockers, presynaptic adrenergic neuron antagonists, or α_1-adrenergic antagonists, depending on their mechanism of action. These drugs are rarely used clinically and little is known about their effects in overdose.

Ganglionic Blockers

Ganglionic blockers, such as trimethaphan, inhibit impulse transmission down the postganglionic sympathetic, as well as parasympathetic nerves, decreasing vascular tone, cardiac output, and blood pressure. In overdose, the exaggerated hypotensive response should respond well to intravenous crystalloid boluses and, if needed, a direct-acting vasopressor such as norepinephrine.

Presynaptic Adrenergic Neuron Antagonists

These drugs exert their sympatholytic action by decreasing norepinephrine release from presynaptic nerve terminals. In overdose, an extension of their pharmacologic effects is expected. Severe orthostatic hypotension should be anticipated and treated with intravenous crystalloid boluses and a direct-acting vasopressor. If reserpine is involved, significant CNS depression should also be anticipated.

Peripheral α_1-Adrenergic Antagonists

The selective α_1-adrenergic antagonists include prazosin, terazosin, and doxazosin. The α_1 receptor is a postsynaptic receptor primarily located on vascular smooth muscle, although it is also found in the eye and in the GI and genitourinary tracts. In overdose, hypotension and CNS depression—ranging from lethargy to coma—are reported. Treatment is with supportive care, including intravenous fluid boluses and a vasopressor. Dopamine might be effective.

DIRECT VASODILATORS

The direct vasodilators include hydralazine, minoxidil, diazoxide, and sodium nitroprusside.

Adverse effects associated with daily hydralazine use include several immunologic phenomena, such as hemolytic anemia, vasculitis, acute glomerulonephritis, and, most notably, a lupuslike syndrome. Minoxidil may cause electrocardiographic changes, both in therapeutic doses and in overdose. Sinus tachycardia, ST-segment depressions, and T-wave inversions are reported. The significance of these changes is unknown; they typically resolve with either continued therapy or as other toxic manifestations resolve.

The toxic manifestations are an extension of the recognized pharmacologic actions. Symptoms may include lightheadedness, syncope, palpitations, and nausea. Signs may be isolated to tachycardia alone, flushing, or alterations in mental status, which is related to the degree of hypotension.

After appropriate GI decontamination, routine supportive care should be performed, with special consideration to maintaining adequate mean arterial pressure. If intravenous crystalloid boluses are insufficient, a peripherally acting α-adrenergic agonist vasopressor such as norepinephrine or phenylephrine is an appropriate next therapy. Dopamine and epinephrine should be avoided to prevent an exaggerated myocardial response and tachycardia from β-adrenergic stimulation.

Sodium nitroprusside exerts its vasodilatory effects after spontaneously releasing the vasodilator nitric oxide into the blood. The nitroprusside molecule also contains 5 cyanide radicals that are generally gradually released, but which, on occasion, can produce cyanide toxicity. Physiologic methemoglobin can bind the liberated cyanide and rhodanese can then convert the cyanide to thiocyanate. Infusion of nitroprusside at a rate of more than 1.5 mg/kg administered over a few hours, or more than 4 μg/kg/min for more than 12 hours, may overwhelm the capacity of rhodanese for detoxifying cyanide. Signs and symptoms of cyanide toxicity include alteration in mental status, anion gap metabolic acidosis, and, in late stages, hemodynamic instability. (Chapter 121 provides a complete discussion of cyanide.)

Thiocyanate is almost exclusively renally eliminated, with an elimination half-life of 3–7 days. It is postulated that a continuous sodium nitroprusside infusion of 2.5 μg/kg/min in patients with normal renal function could produce thiocyanate toxicity within 7–14 days, although it may be as short as 3–6 days or as little as 1 μg/kg/min in patients with chronic renal insufficiency who are not receiving hemodialysis. The symptoms of thiocyanate toxicity begin to appear at serum concentrations of 1 mmol/L (60 μg/mL), are very nonspecific, and may include nausea, vomiting, fatigue, dizziness, confusion, delirium, and seizures. Thiocyanate toxicity can produce life-threatening effects such as hemodynamic and intracranial pressure elevation. An anion gap metabolic acidosis or hemodynamic instability does not occur with thiocyanate toxicity. Although cyanide or thiocyanate concentrations are not typically useful in the management of cyanide toxicity, they may be beneficial for monitoring critically ill patients who are at risk of thiocyanate poisoning. Hemodialysis is the treatment of choice for patients with severe clinical manifestations of thiocyanate toxicity.

DIURETICS

Diuretics can be divided into three main groups: (a) the thiazides and related compounds, including hydrochlorothiazide and chlorthalidone; (b) the loop diuretics, including furosemide, bumetanide, and ethacrynic acid; and (c) the potassium-sparing diuretics, including amiloride, triamterene, and spirono-

lactone. Two other groups of diuretics—the carbonic anhydrase inhibitors, such as acetazolamide, and osmotic diuretics, such as mannitol—are not used as antihypertensive therapy.

The thiazides produce their diuretic effect by inhibition of sodium and chloride reabsorption in the distal convoluted tubule. Loop diuretics, in contrast, inhibit the coupled transport of sodium, potassium, and chloride in the thick ascending limb of the loop of Henle.

The most common toxicity associated with diuretics is metabolic alkalosis and occurs during chronic therapy or overuse. Hyponatremia (<120 mEq/L) presents as headache, nausea, vomiting, confusion, seizures, or coma. Pontine demyelination has been reported during rapid correction of severe hyponatremia secondary to diuretic abuse (Chap. 17). Other electrolyte abnormalities include hypokalemia and hypomagnesemia, which may precipitate ventricular dysrhythmias and sudden death associated.

Despite the widespread use of these drugs, acute overdoses are distinctly rare. Major signs and symptoms include GI distress, brisk diuresis, possible hypovolemia and electrolyte abnormalities, and altered mental status. Assessment should focus on fluid and electrolyte status, which should be corrected as needed.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors (ACEIs) are among the most widely prescribed antihypertensives. In general, these drugs are well absorbed from the GI tract, reaching peak serum concentrations within 1–4 hours. Enalapril and ramipril are prodrugs and require hepatic metabolism to produce their active forms. These drugs are primarily eliminated via the kidneys.

All ACEIs bind directly to the active site of angiotensin-converting enzyme, which is found in the lung and vascular endothelium, preventing the conversion of angiotensin I to angiotensin II. Because angiotensin II is a potent vasoconstrictor and stimulant of aldosterone secretion, vasodilation, decreased peripheral vascular resistance, decreased blood pressure, increased cardiac output, and a relative increase in renal, cerebral, and coronary blood flow occur. ACEIs should not be used during pregnancy.

ACEI-Induced Angioedema

Angioedema is an inflammatory reaction in which there is increased capillary blood flow and permeability resulting in an increase in interstitial fluid. If this process is confined to the superficial dermis, urticaria develops, whereas if the deeper layers of the dermis or subcutaneous tissue are involved, angioedema results. Angioedema most commonly involves the periorbital, perioral, or oropharyngeal tissues. This swelling may progress rapidly over minutes and result in complete airway obstruction and death. The pathogenesis of acquired angioedema involves multiple vasoactive substances, including bradykinin, and is not IgE-mediated.

One-third of cases may occur at any time after the first few days of therapy, even after years. Because of the propensity to involve the tongue, face, and oropharynx, the airway must remain the primary focus of management. The most important aspect of airway management in patients suffering from ACEI-induced angioedema, however, is early risk assessment for airway ob-

struction followed by rapid intervention, prior to severe, obstructive swelling developing.

Therapy typically includes the standard medications used for anaphylaxis, such as subcutaneous epinephrine, intravenous diphenhydramine, and corticosteroids. However, because ACEI-induced angioedema is not an antibody-mediated allergic phenomenon, these interventions will probably have limited efficacy so they should not be assumed or relied on to avoid definitive airway protection. All patients with mild or quickly resolving angioedema should be observed for several hours to ensure that the swelling does not progress or return. Outpatient therapy with a short course of oral antihistamines and corticosteroids is appropriate. Such patients should be instructed to discontinue ACEI therapy permanently and to consult their primary physician about other antihypertensive options. Because this is a mechanistic and not allergic adverse effect, the use of any other ACEIs is contraindicated.

ACEI Overdose

The toxicity of ACEIs in overdose appears to be limited. Hypotension may occur in select patients but deaths are rarely reported in isolated ACEI ingestions. Treatment is supportive and symptomatic. Activated charcoal alone is sufficient in most cases and should be given as long as no contraindications exist. Intravenous crystalloid boluses are often effective in correcting hypotension, although in rare cases, catecholamines may be required. Naloxone may also be effective in reversing the hypotensive effects of ACEIs.

ANGIOTENSIN II RECEPTOR BLOCKERS

These drugs are rapidly absorbed from the GI tract, reaching peak serum concentrations in 1–4 hours, and they are either eliminated unchanged in the feces, or, after undergoing hepatic metabolism via the mixed function oxidase system, are eliminated in the bile.

Angiotensin receptor blockers (ARBs) act by antagonizing angiotensin II at the type 1 angiotensin (AT-1) receptor. Like ACEIs, ARBs should never be used by pregnant patients because of their teratogenic potential.

There are no published reports of overdoses, but hypotension should be anticipated and treated with intravenous crystalloid therapy and traditional catecholamines. Rare cases of angioedema associated with ARB therapy are reported.

61 Antidysrhythmics

The term *dysrhythmia* encompasses an array of abnormal cardiac rhythms that range in clinical significance from merely annoying to instantly life-threatening. An abundance of antidysrhythmics have been developed, each attempting to alter specific electrophysiologic components of the cardiac impulse generating or conducting system. In addition to the predictable, mechanism-based adverse effect of each drug, unique and often unanticipated effects also occur. Experience with overdose of many of these drugs is limited, and management is generally based on the underlying pharmacologic principles, existing case reports, and the experimental literature.

CLASSIFICATION OF ANTIDYSRHYTHMICS

Antidysrhythmics modify impulse generation and conduction by interacting with various membrane sodium, potassium, and calcium ion channels. Generally, antidysrhythmics alter electrophysiologic effects either through blockade of the channel pore or, more commonly, by modification of its gating mechanism. The description of an antidysrhythmic as a specific "channel blocker" or "channel opener," although representative of a specific action of that drug, is often incomplete because many of these drugs are active at other channels or on other cells.

The Vaughan Williams (VW) classification of antidysrhythmics by electrophysiologic properties emphasizes the connection between the basic electrophysiologic actions and the antidysrhythmic effects. Although there are limitations to this system, it remains widely used in clinical practice.

Class I Agents

All antidysrhythmics in VW class I (A, B, and C) alter Na^+ conductance through cardiac voltage-gated, fast inward Na^+ channels (Table 61–1). These drugs bind to the Na^+ channels and slow their recovery from the open or inactivated state to the resting state. This slows the rise of phase 0 of the cellular action potential, which correlates with a reduction in the rate of depolarization of the myocardial cell (or V_{max}). Similarly, conduction through the myocardium is slowed, producing a measurable prolongation of the QRS complex on the surface electrocardiogram. Correspondingly, slowed intramyocardial conduction is associated with reduced contractility, manifesting as negative inotropy. The differences among class I drugs are directly related to their pharmacologic relationships with the Na^+ channel.

Some of the class I drugs, particularly those in class IA, have important effects on cardiac potassium channels. Slowing of potassium efflux thus prolongs the duration of the action potential and accounts for the persistence of absolute or relative refractoriness, or the time during which the cell is incapable or less capable of redepolarization. This effect produces QTc prolongation on the surface electrocardiogram, and predisposes to the triggering of polymorphic ventricular tachycardia.

Class IA Antidysrhythmics: Procainamide, Quinidine, and Disopyramide

Table 61–1 discusses the pharmacology and expected clinical findings following overdose with a class IA antidysrhythmic.

TABLE 61–1. Antidysrhythmics: Pharmacology, Pharmacokinetics, and Adverse Effects

Drug	Route	Primary Route of Elimination	Vaughan-Williams Classification	Channel Blockade	Adverse Effects and Complicating Factors	Volume Distribution (L/Kg)	Protein Binding (%)
Disopyramide	PO	Liver, kidney	Class IA	Na^+, K^+, Ca^{2+}	Congestive heart failure, negative inotropic effects, anticholinergic, torsades de pointes, heart block, hypoglycemia	0.59 ± 0.15	35–95 depending on plasma concentration
Procainamide	IV, PO	50–60% unchanged in kidney, liver, active metabolite	Class IA	Na^+, K^+	Hypotension, QRS widening, fever, SLE-like syndrome, torsades de pointes	1.9 ± 0.3	16 ± 9
Quinidine	PO	Liver, kidney, 10–20% unchanged	Class IA	Na^+, K^+, Ca^{2+}	Heart block, severe sinus node dysfunction, prolonged QT syndrome, hypotension, hypoglycemia, torsades de pointes, thrombocytopenia, ↑ digoxin concentrations	2.7 ± 1.2	87 ± 3
Lidocaine	SC, IV, PO	Liver, active metabolite	Class IB	Na^+	Fatigue, agitation, paresthesias, seizures, hallucinations, rarely bundle branch block	1.1 ± 0.4	70 ± 5
Mexiletine	IV, PO	Liver	Class IB	Na^+	See lidocaine	4.9 ± 0.5	63 ± 3
Moricizine	PO	Liver	Class IB	Na^+	↑ Mortality after myocardial infarction, bradycardia, CHF, ventricular fibrillation, ventricular tachycardia	?	95

Phenytoin	IV, PO	Liver	Class IB	Na^+	Hypotension and asystole related to IV propylene glycol infusion (diluent), nystagmus, ataxia	0.64 ± 0.04	89 ± 23
Tocainide	IV, PO	Kidney, liver	Class IB	Na^+	See lidocaine, aplastic anemia, interstitial pneumonia	3.0 ± 0.2	10 ± 15
Flecainide	IV, PO	Liver 75%, kidney 25%	Class IC	Na^+, Ca^{2+}, K^+	Negative inotropic effects, bradycardia, heart block, ventricular fibrillation, ventricular tachycardia, neutropenia	4.9 ± 0.4	61 ± 10
Propafenone	IV, PO	Liver	Class IC	Na^+, K^+	Asthma, congestive heart failure, hypoglycemia, AV block, QRS prolongation, bradycardia, ventricular fibrillation, ventricular tachycardia	3.6 ± 2.1	85 ± 95
β-Adrenergic antagonists	IV, PO	Liver	Class II	β-Adrenergic receptor	Congestive heart failure, asthma, hypoglycemia, Raynaud's disease		
Amiodarone	IV, PO	Liver	Class III	Na^+, Ca^{2+}, K^+	Negative inotropic effects, pulmonary fibrosis, corneal microdeposits, thyroid abnormalities, hepatitis photosensitivity, ↑ diltiazem, quinidine, procainamide, flecainide, digoxin concentrations	66 ± 44	99.98 ± 0.01

(continued)

TABLE 61–1. Antidysrhythmics: Pharmacology, Pharmacokinetics, and Adverse Effects *(continued)*

Drug	Route	Primary Route of Elimination	Vaughan-Williams Classification	Channel Blockade	Adverse Effects and Complicating Factors	Volume Distribution (L/Kg)	Protein Binding (%)
Bretylium	IV, IM	Kidney	Class III	K^+	Hypertension followed by hypotension, nausea, and vomiting	5.9 ± 0.8	(0–8)
Dofetilide	IV, PO	Kidney	Class III	K^+	Torsades de pointes	3.6 ± 0.8	64
Ibutilide	IV	Kidney	Class III	K^+, Na^+ opener	Torsades de pointes, heart block	11	40
Calcium channel blockers	IV, PO	Liver	Class IV	Ca^{2+}	Asystole (if used IV with IV β-adrenergic receptor antagonists), AV block, hypotension, congestive heart failure, constipation, ↑ digoxin concentrations		
Adenosine	IV	All cells (adenosine deaminase)	Not classified	Nucleoside-specific G protein–coupled adenosine receptors, ↑ Ca^{2+} currents activate ACh-sensitive K^+ current	Transient asystole <5 s, chest pain, dyspnea, atrial fibrillation, ↓ BP, effects potentiated by dipyridamole and in heart transplant patients, ↑ dose needed with methylxanthine use		

Management

Following airway evaluation and intravenous line placement, the 12-lead ECG and continuous electrocardiographic monitoring are of paramount importance. Appropriate GI decontamination is recommended when the patient is stabilized and should include consideration of whole-bowel irrigation if a sustained-release preparation is involved.

For patients with widening of the QRS complex duration, bolus administration of intravenous hypertonic sodium bicarbonate is indicated. Depolarization is accelerated and the QRS complex duration is reduced by enhancing rapid sodium ion influx through the myocardial sodium channels. Class IA antidysrhythmic-induced hypotension is treated primarily with rapid crystalloid infusion so as to expand the patient's intravascular volume and to simultaneously increase myocardial contractility (ie, enhanced Starling force). Patients with stable ventricular dysrhythmias occurring in the setting of class IA antidysrhythmic poisoning are usually treated with hypertonic sodium bicarbonate or lidocaine. Magnesium sulfate is typically helpful in treating torsades de pointes. Drugs that must be avoided in treating patients with dysrhythmias associated with class IA poisoning include other class IA and IC agents, as well as the β-adrenergic antagonists and calcium channel blockers, all of which may exacerbate conduction abnormalities. There is no clinical evidence to support the use of hemodialysis or hemoperfusion for quinidine or disopyramide poisoning.

Class IB Antidysrhythmics: Lidocaine, Tocainide, Mexiletine, and Moricizine

Because of its rapid entry into the brain, acute lidocaine poisoning typically produces CNS dysfunction, particularly seizures, as its initial manifestation. Concomitant respiratory arrest generally occurs. Shortly following the CNS effects, depression in the intrinsic cardiac pacemakers leads to sinus arrest, atrioventricular (AV) block, intraventricular conduction delay, hypotension, and/or cardiac arrest. If the patient is supported through this period, the drug distributes from the heart and spontaneous cardiac function returns.

Nonmassive acute lidocaine toxicity is generally related to excessive or inappropriate therapeutic dosing. Common settings include intravenous administration when the intended route was subcutaneous, inadvertent excessive subcutaneous administration during laceration repair, or swallowing of viscous oral lidocaine. The typical CNS manifestations of nonmassive acute lidocaine poisoning include drowsiness, weakness, a sensation of "drifting away," euphoria, dysphoria, diplopia, decreased hearing, paresthesias, muscle fasciculations, and seizures. The more severe of these effects develop when blood lidocaine concentrations exceed 5 μg/mL and are often preceded by paresthesias or somnolence. Any of these symptoms should prompt the clinician to examine the patient's medication administration history or drug-infusion rate. Apnea and seizures, as well as hypotonia in neonates, are reported to result from lidocaine toxicity and may occur at lower serum concentrations.

It should be noted that when lidocaine is absorbed from the oropharynx, nongastrointestinal mucosal surfaces, skin, or subcutaneous tissues, hepatic metabolism is bypassed, resulting in increased systemic bioavailability of the parent compound.

Table 61–1 discusses the pharmacology and expected clinical findings following overdose with a class IB antidysrhythmic.

Treatment

The focus of the initial management for intravenous lidocaine-induced cardiac arrest is continuous cardiopulmonary resuscitation to allow lidocaine to redistribute away from the heart. Outside of this setting, management of hemodynamic compromise includes fluid replacement and other conventional strategies. Resistant hypotension may require dopamine or norepinephrine administration. Lidocaine-induced seizures, or those related to lidocaine analogs, are generally brief in nature and do not require specific therapy. For patients requiring treatment, an intravenous benzodiazepine generally suffices. Enhanced elimination techniques are limited following intravenous poisoning because of the rapid time course of poisoning.

Class IC Antidysrhythmics: Flecainide and Propafenone

Table 61–1 discusses the pharmacology and expected clinical findings following overdose with a class IC antidysrhythmic.

Altered mental status and seizures are the most frequent noncardiac consequences. Typical electrocardiogram findings include prolongation of the PR interval, QRS duration, or QTc, in addition to bradycardia, premature ventricular contractions, wide complex tachycardia, and ventricular fibrillation.

Treatment

Initial stabilization should include standard management strategies for hypotension and seizures. Additionally, therapy for hypotension, and for the electrocardiographic manifestations of class IC poisoning, includes intravenous hypertonic sodium bicarbonate to overcome the Na^+ channel blockade. The administration of other class IC or IA antidysrhythmics is clearly contraindicated because of their additive blockade of the Na^+ channel. However, amiodarone has been successful in the setting of ventricular fibrillation refractory to other therapy. Extracorporeal removal is not generally expected to be beneficial for patients with class IC poisoning.

Class III Antidysrhythmics: Amiodarone, Dofetilide, and Ibutilide

The class III antidysrhythmics prevent and terminate reentrant dysrhythmias by prolonging the action potential duration and effective refractory period without slowing conduction velocity. This is caused by blockade of the rapidly activating component of the delayed rectifier potassium current, which is responsible for repolarization. Table 61–1 discusses the pharmacology and expected clinical findings following overdose with a class III antidysrhythmic.

The common electrocardiographic effects of the class III agents at therapeutic doses are prolongation of the PR and QTc intervals and abnormal T and U waves (Chap. 23).

Amiodarone

Amiodarone is structurally similar to both thyroxine and procainamide. Forty percent of the molecular weight is iodine. In addition to its class III antidysrhythmic effects, amiodarone also has weak α- and β-adrenergic antagonist activity and can block both L-type calcium channels and inactivated sodium channels. Amiodarone is slowly absorbed by the oral route and concentrates in the liver, lung, and adipose tissue. Steady-state pharmacokinetics may not occur for more than a month, and the elimination half-life is 2 months. Amio-

darone is metabolized via cytochrome P450 (CYP) 3A4 to desethylamiodarone, which has comparable activity to the parent compound. Elimination is through biliary excretion and virtually none is renally cleared.

Therapeutic oral doses prolong PR and QTc intervals but not the QRS complex. Intravenous dosing may produce hypotension and a prolongation of the PR interval, but has few other electrocardiographic manifestations. Ventricular dysrhythmias and sinus bradycardia are the most serious cardiac complications of therapeutic doses of amiodarone. The ability of amiodarone to compete for P-glycoprotein is responsible for several consequential drug effects, including elevated digoxin and cyclosporine concentrations, and enhanced anticoagulation effectiveness of warfarin.

The diverse complications associated with long-term therapy do not occur following short-term intravenous use. Chronic therapy with oral amiodarone is associated with substantial pulmonary, thyroid, corneal, hepatic, and cutaneous toxicity, organs in which it bioaccumulates.

Treatment

Treatment experience with class III drug overdose is limited. Torsades de pointes may be treated with magnesium, isoproterenol, or overdrive pacing. Hemodialysis is not expected to be beneficial, although multiple-dose activated charcoal and charcoal hemoperfusion may be of help if used immediately following overdose.

UNCLASSIFIED: ADENOSINE

The effects of adenosine are mediated by its interaction with specific G protein–coupled adenosine (A_1) receptors that activate acetylcholine-sensitive outward K^+ current in the atrium, sinus nodes, and AV nodes. The resultant hyperpolarization reduces the rate of cellular firing.

Adverse effects of adenosine administration are very common and include transient asystole, dyspnea, chest tightness, flushing, hypotension, and atrial fibrillation. Fortunately, most of the adverse effects of adenosine are transitory because of its rapid metabolism to inosine by both extracellular and intracellular deaminases. The clinical effects are potentiated by dipyridamole, an adenosine uptake inhibitor, and in cardiac transplant recipients, who develop denervation hypersensitivity. Methylxanthines may produce adenosine receptor blockade, and in this setting (Chap. 63), larger-than-usual doses of adenosine are required to produce an antidysrhythmic effect. Overdose of adenosine is not reported. Treatment is supportive because of the rapid elimination of the drug.

62 Cardioactive Steroids

Cardioactive steroids are among the many treatments used for congestive heart failure, and for the control of the ventricular response rate in atrial tachydysrhythmias. The most commonly prescribed cardioactive steroid in the United States is digoxin. Because of the narrow therapeutic-to-toxic index and widespread use of these preparations, both acute and chronic toxicity remains an important problem.

Older adults are at particular risk for toxicity, either from interactions of the cardioactive steroids with their chronic regimen of medications, or indirectly because of an alteration in the absorption or elimination kinetics of their therapeutic cardioactive steroid. Drug–drug interactions may change cardioactive steroid clearance in the liver or kidney, from altered binding to p-glycoprotein, or from coingested medications that increase their bioavailability. Cardioactive steroid toxicity may also result from exposure to certain plants or animals. Documented sources of cardioactive steroids include oleander (*Nerium oleander*), yellow oleander (*Thevetia peruviana*), foxglove (*Digitalis* spp), lily of the valley (*Convallaria majalis*), dogbane (*Apocynum cannabinum*), and red squill (*Urginea maritima*), as well as the dried secretion of the *Bufo marinus* toad.

PHARMACOKINETICS

The correlation between clinical effects and serum concentrations is based on steady-state concentrations, which are dependent on many absorption, distribution, and elimination factors (Table 62–1). Obtaining a serum digoxin concentration before 6 hours after an ingestion (the time at which the tissue concentration has peaked) gives a misleadingly high serum concentration, a result of its biphasic distribution. The terminal elimination phase has a half-life of approximately 36 hours.

Hypokalemia resulting from a variety of mechanisms, such as the use of loop diuretics, poor dietary intake, diarrhea, and the administration of potassium-binding resins, enhances the effects of cardioactive steroids on the myocardium and is associated with dysrhythmias at lower serum cardioactive steroid concentrations.

Drug interactions between digoxin and quinidine, verapamil, diltiazem, carvedilol, amiodarone, and spironolactone are common. These interactions occur as a result of reduced renal excretion or inactivation of P-glycoproteins. Inhibition by antibiotics (particularly by the macrolides) of the normal metabolism of digoxin in the GI tract by *Eubacterium lentum*, may increase the digoxin bioavailability.

MECHANISMS OF ACTION AND PATHOPHYSIOLOGY

Electrophysiologic Effects on Inotropy

Cardioactive steroids inhibit Na^+-K^+-ATPase during repolarization by the membrane. This ultimately reduces Ca^{2+} extrusion from the cell and enhances

TABLE 62–1. Pharmacology of Selected Cardioactive Steroids

Pharmacology	Digoxin	Digitoxin
Onset of action		
Oral	1.5–6 h	3–6 h
IV	5–30 min	30 min–2 h
Maximal effect		
Oral	4–6 h	6–12 h
IV	1.5–3 h	4–8 h
Intestinal absorption	40–90% (mean 75%)	>95%
Plasma protein binding	25%	97%
Volume of distribution	6–7 L/kg (adults) 16 L/kg (infants) 10 L/kg (neonates) 4–5 L/kg (adults with renal failure)	0.6 L/kg (adults)
Elimination half-life	1.6 days	6–7 days
Route of elimination	Renal (60–80%), with limited hepatic metabolism	Hepatic metabolism (80%)
Enterohepatic circulation	7%	26%

the Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum during systole. This increases the force of contraction of the cardiac muscle.

Effects on Cardiac Conduction

At therapeutic concentrations, cardioactive steroids also increase automaticity and shorten the repolarization intervals of the atria and ventricles. This is mediated both indirectly via an enhancement in vagally mediated parasympathetic tone and directly by depression of this tissue. This is reflected on the ECG as PR interval prolongation (part of "digitalis effect"). The effects of cardioactive steroids on ventricular repolarization are related to the elevated intracellular Ca^{2+} and manifest on the ECG as QTc shortening and ST segment and T-wave forces opposite in direction to the major QRS forces. The last effect results in the characteristic scooping of the ST segments (the second part of which is referred to as "digitalis effect"). Excessive increases in intracellular Ca^{2+} result in delayed afterdepolarizations, which may lead to premature ventricular contraction or ventricular tachydysrhythmias (Chap. 23). Hypokalemia inhibits Na^+-K^+-ATPase activity and enhances the effect of the cardioactive steroids.

Effects of Cardioactive Steroids on the Autonomic Nervous System

Cardioactive steroids affect the parasympathetic system by increasing the release of acetylcholine from vagal fibers.

CLINICAL MANIFESTATIONS

Both adults and children with acute cardioactive steroid poisoning present in a similar manner, as do adults and children with chronic poisoning. However,

the clinical manifestations in both adults and children vary based on the chronicity of the exposure.

Noncardiac Manifestations

Acute Toxicity

Following an asymptomatic period of several minutes to several hours, the first symptom is typically nausea, vomiting, or abdominal pain. Central nervous system effects of acute toxicity may include lethargy, confusion, and weakness that are not caused by hemodynamic changes.

Chronic Toxicity

Chronic toxicity is often difficult to diagnose as a result of its insidious development and protean manifestations. Symptoms may include those that occur with acute poisonings; however, they are often less obvious. Gastrointestinal symptoms, as well as delirium, confusion, disorientation, drowsiness, headache, visual disturbances (eg, halos), hallucinations, or rarely, seizures can occur.

Electrolyte Abnormalities

Hyperkalemia has important prognostic implications in acute overdose, as the serum potassium concentration is a better predictor of lethality than either the initial ECG changes or the serum cardioactive steroid concentration. Note that simply correcting the hyperkalemia does not increase patient survival; it is a marker of, and not the cause of, the morbidity and mortality.

Cardiac Manifestations

The alterations in cardiac rate and rhythm occurring with cardioactive steroid poisoning can produce almost every known type of dysrhythmia, with the exception of the rapidly conducted supraventricular tachydysrhythmias. An ectopic ventricular rhythm is generally the first and most frequent sign of toxicity. Although no dysrhythmia is pathognomic of cardioactive steroid toxicity, toxicity should be suspected when bidirectional ventricular tachycardia or atrial tachycardia with high-degree A-V block is present.

Acute Toxicity

The initial increased vagal tone at the sinoatrial (SA) and atrioventricular (AV) nodes results in an atropine-responsive bradydysrhythmia.

Chronic Toxicity

Bradydysrhythmias that appear later in acute poisonings, or those occurring in patients with chronic cardioactive steroid toxicity, occur by direct actions of the drug on the heart and often are minimally responsive, or cannot be corrected by the administration of atropine. Ventricular tachydysrhythmias are more common in patients with chronic or late acute poisoning than they are in early acute poisoning.

DIAGNOSTIC TESTING

Properly obtained and interpreted serum digoxin concentrations significantly aid in the management of patients with digoxin toxicity, as well as in the management of those poisoned by several other cardioactive steroids. Re-

gardless of the serum concentration used, it must be interpreted in relation to the clinical condition of the patient, the relationship of the time of obtaining the blood sample to that of the last dose, metabolic abnormalities, including hyper- or hypokalemia, hypomagnesemia, hypercalcemia, hypernatremia, alkalosis, hypothyroidism, hypoxemia, catecholamines, and the use of calcium channel blockers, quinidine, amiodarone, or diuretics.

It is **inaccurate** to use the therapeutic range of digoxin of 0.5–2.0 ng/mL as the sole indicator of toxicity. In general, patients with pharmaceutical digoxin toxicity have clinical findings and mean serum concentrations above 2 ng/mL, measured at least 6 hours postingestion for digoxin.

Other cardioactive steroids may cross-react with the digoxin assay available in most hospitals. However, there is currently no known clinical utility to the actual concentration, other than to confirm its presence. A negative concentration does not exclude the presence of a nondigoxin cardioactive steroid.

Serum concentrations of digoxin are measured in 1 of 2 ways: free digoxin or total digoxin. Under normal circumstances, measuring total digoxin in the serum is sufficient, as serum concentrations are predictive of cardiac concentrations. However, after the use of digoxin-specific Fab (which remains almost entirely within the intravascular space [volume of distribution (Vd) of 0.40 L/kg]) there is a large elevation in total cardioactive steroid concentrations because the cardioactive steroid is drawn from the tissues and complexes with the antibody fragment, thus trapping the cardioactive steroid in the intravascular space. Then only free digoxin concentrations are meaningful.

Endogenous Digoxinlike Immunoreactive Substance

Some patients who are not receiving a cardioactive steroid may have a positive digoxin assay as a result of an endogenous substance that is structurally and functionally similar to the prescribed cardioactive steroids. This endogenous digoxinlike immunoreactive substance (EDLIS) is described in patients with increased inotropic need or reduced renal clearance, including neonates, patients with renal insufficiency, liver disease, or hypothermia, or pregnant patients, among others.

THERAPY

Management Overview

Initial treatment of a patient with acute cardioactive steroid poisoning includes providing general supportive care, discontinuing cardioactive steroid therapy, preventing further exposure, preventing further GI absorption, monitoring for dysrhythmias, determining electrolyte and digoxin concentrations, administering digoxin-specific antibodies fragments, and treating specific complications such as dysrhythmias and electrolyte abnormalities.

Gastrointestinal Decontamination

Initial treatment should be directed toward prevention of further GI absorption. Emesis and lavage are not generally valuable. Because many cardioactive steroids such as digitoxin and digoxin are recirculated enterohepatically and enteroenterically, late as well as repeated activated charcoal administration (1 g/kg body weight every 2–4 hours for up to 4 doses) may be beneficial in reducing serum concentrations especially when antidote is unavailable. Patients with chronic ingestion do not usually benefit from these GI decontamination techniques.

Advanced Management

Digoxin-Specific Antibody Fragments

The standard of care for patients with life-threatening cardioactive steroid toxicity is the use of digoxin-specific antibody fragments. Although the drug itself is expensive, its expense is far outweighed by obviating the need, risk, and expense of long-term ICU stays, and of repetitive evaluation of potassium and digoxin concentrations. Table 62–2 lists the indications and dose for digoxin-specific Fab.

Additional Cardiac Therapies

In patients with symptomatic supraventricular bradydysrhythmias or high degrees of AV block, atropine 0.5 mg should be administered intravenously to an adult, or 0.02 mg/kg with a minimum of 0.1 mg to a child. In the event that digoxin-specific fragments are not immediately available, the secondary drugs for the management of ventricular irritability include phenytoin and lidocaine at conventional doses.

Pacemakers and Cardioversion

External pacemakers may have limited utility in cases of refractory bradycardia. However, insertion of a transvenous pacemaker is contraindicated because it can provoke lethal dysrhythmias. Cardioversion should be reserved for the most consequential, life-threatening dysrhythmias and is rarely necessary when digoxin-specific Fab is available.

Electrolyte Therapy

Potassium

Hypokalemia, most commonly from therapeutic diuretic use, can exacerbate cardioactive steroid cardiotoxicity, and simple correction may quell the tachydysrhythmia. Digoxin-specific Fab administration generally should not be used until the hypokalemia is corrected because the reinstitution of Na^+-K^+-ATPase function may cause profound hypokalemia.

In the presence of acute cardioactive steroid toxicity when potassium exceeds 5.0 mEq/L, digoxin-specific antibodies are indicated. When marked hyperkalemia develops in conjunction with ECG evidence of hyperkalemia, and if digoxin-specific Fab is not available immediately, an attempt should be made to lower the serum potassium with IV insulin, dextrose, sodium bicarbonate, and oral administration of the ion-exchange resins sodium polystyrene sulfonate. *Calcium chloride is beneficial in most hyperkalemic patients, but in the presence of cardioactive steroid poisoning, calcium salts may be disastrous, as intracellular hypercalcemia is already present.* The purported mechanism is augmented intracellular cytoplasmic Ca^{2+}.

Magnesium

Hypomagnesemia may also occur in cardioactive steroid–poisoned patients secondary to long-term diuretic use to treat congestive heart failure. Concomitant hypomagnesemia may result in refractory hypokalemia despite potassium replacement. Additionally, magnesium may suppress ectopy, although this treatment is only temporizing until digoxin-specific Fab is available for definitive therapy A common regimen uses 2 g of magnesium sulfate IV over

TABLE 62–2. Indications for Administration of Digoxin-Specific Antibody Fragments

Any potential digoxin-related life-threatening dysrhythmia
Potassium concentration >5.0 mEq/L in setting of acute digoxin poisoning
Chronic digoxin poisoning with dysrhythmias, significant gastrointestinal symptoms, or acute onset of significantly altered mental status, or renal insufficiency
Serum digoxin concentration (SDC) ≥15 ng/mL at any time, or ≥10 ng/mL 6 h postingestion
Ingestion of 10 mg in adult
Ingestion of 4 mg in a child
To aid in treatment of suspected cardioactive steroid poisoning without a confirmatory level
Poisoning by nondigoxin cardioactive steroid
Digoxin-specific Fab dosing (round up vial calculation)
$\text{No. of vials} = \frac{\text{SDC (ng/mL)} \times \text{Pt Wt (kg)}}{100}$
$\text{No. of vials} = \frac{\text{Amount ingested (mg)}}{0.5\ \text{(mg/vial)}} = 80\%\ \text{bioavailability}$
Empiric therapy for acute poisoning:
10–20 vials (adult or pediatric)
Empiric therapy for chronic poisoning:
Adult—3–6 vials
Pediatric—1–2 vials

20 minutes in an adult, or 25–50 mg/kg/dose to a maximum of 2 g in a child. Following stabilization, a patient with severe hypomagnesemia may require a magnesium infusion of 1–2 g/h in an adult or 25–50 mg/kg/h to a maximum of 2 g in a child with serial monitoring of serum magnesium concentrations, telemetry, vital signs, and deep-tendon reflexes. Magnesium is contraindicated in the setting of bradycardia or atrioventricular block, preexisting hypermagnesemia, and renal insufficiency or failure.

Extracorporal Removal

Forced diuresis, hemoperfusion, and hemodialysis are ineffective in enhancing the elimination of digoxin because of its large volume of distribution (4–10 L/kg).

Digoxin-Specific Antibody Fragments (Fab)

Digoxin-specific antibody fragments are indicated for the management of patients with toxicity related to digoxin, digitoxin, and all natural cardioactive steroids (CAS), such as oleander, squill, and toad venom. Digoxin-specific antibody fragments have an excellent efficacy and safety profile and should be administered early in both established and suspected digoxin and CAS poisoning.

BACKGROUND

Digoxin is used as a hapten and joined to an immunogenic protein carrier such as albumin, which is then used to immunize sheep and generate antibodies. The antibodies are separated and highly purified to retain the digoxin antibodies while removing the antibodies to the albumin and all other extraneous proteins. These antibodies have a high affinity for digoxin and sufficient cross-reactivity with digitoxin to be clinically useful for the treatment of poisoning with that agent as well.

To make these antibodies safe and effective in humans, whole IgG antidigoxin antibodies are cleaved with papain, yielding 2 antigen-binding fragments (Fab) with a molecular weight of 50,000 daltons each and 1 Fc fragment. Two similar commercial products (Digibind and DigiFab), are now available.

PHARMACOLOGY

Immediately following IV administration, digoxin-specific antibody fragments bind intravascular free digoxin. Unbound antibodies then diffuse into the interstitial space, binding free digoxin there. A concentration gradient is then established to facilitate movement of the free intracellular digoxin and digoxin that is dissociated from its binding sites (the external surface of Na^+-K^+-ATPase) in the heart and in skeletal muscle, into the interstitial or intravascular spaces.

PHARMACOKINETICS

At 30 minutes after infusion of digoxin-specific antibody fragments, the free digoxin serum concentration is below the level of detection of the assay. The elimination half-life of total digoxin averages 19.5 hours. The distribution half-life is 1 hour for unbound digoxin-specific antibody fragment. The systemic clearance of DigiFab is higher than Digibind and accounts for the shorter elimination half life of DigiFab (15 hours vs. 23 hours).

Pharmacokinetic studies in patients with renal failure demonstrate that the half-life of digoxin-specific antibody fragments is prolonged 10-fold with no change in the apparent volume of distribution (Vd). Digoxin-specific antibody fragments serum concentrations remain detectable for 2–3 weeks. Although some digoxin may be released over time, this is rarely clinically significant and occurs in about 10 days.

EFFICACY

Of the 150 patients treated in one study, 148 were evaluated pretreatment for cardiovascular manifestations of toxicity: 79 patients (55%) had high-grade

atrioventricular (AV) block, 68 (46%) had refractory ventricular tachycardia, 49 (33%) had ventricular fibrillation, and 56 (37%) had hyperkalemia. Ninety percent of patients had a response to digoxin-specific antibody fragments within minutes to several hours of administration. Complete resolution of all signs and symptoms of digoxin toxicity occurred in 80% of cases. A partial response was observed in 10% of patients, and of the 15 patients who did not respond, 14 were moribund or actually found not to be digoxin toxic. The spectacular success of digoxin-specific antibody fragments for patients with digoxin toxicity is demonstrated by the fact that of the 56 patients who had cardiac arrest caused by digoxin, 54% survived hospitalization, as compared with 100% mortality before the advent of these fragments. Newborns, infants, and children have all been successfully treated with Digibind.

ADVERSE EFFECTS AND SAFETY

Digoxin-specific antibody fragments also are very safe. Reported adverse effects include hypokalemia as a consequence of reactivation of the Na^+-K^+-ATPase; withdrawal of the inotropic or AV nodal blocking effects of digoxin, leading to congestive heart failure or a rapid ventricular rate in patients with atrial fibrillation; and, rarely, allergic reactions.

Digibind is prepared using digoxin as the hapten. DigiFab is prepared using a digoxin derivative (digoxin-dicarboxymethoxylamine) as the hapten. Affinity chromatography is used to isolate and purify the digoxin-specific antibody fragments following papain digestion. Both products warn that patients with allergies to papain, chymopapain, or other papaya extracts may be at risk for an allergic reaction as trace amounts of these residues may remain in the digoxin-specific antibody fragments. An allergy to sheep protein or patients who have previously received ovine antibodies or ovine Fab may also be at risk for an allergic reaction, although this is not reported.

INDICATIONS FOR DIGOXIN-SPECIFIC FAB

Digoxin-specific antibody fragments are indicated for life-threatening or potentially life-threatening digoxin, digitoxin, or CAS toxicity. See Table 62–2 for details.

ONSET OF RESPONSE

The mean time to initial response from the completion of the digoxin-specific antibody fragments infusion (accomplished over 15 minutes to 2 hours) is 19 minutes (range: 0–60 minutes), and the time to complete response is about 88 minutes (range: 30–360 minutes).

DOSING

See Table 62–2 for dosing.

ADMINISTRATION

According to the manufacturer, Digibind should be administered IV over 30 minutes via a 0.22-micron membrane filter. The 38-mg vial must be reconstituted with 4 mL of sterile water for IV injection, resulting in an isoosmotic solution. Although slow IV infusion over 30 minutes is preferable, in the critically ill Digibind may be given by IV bolus.

Each vial of DigiFab should be reconstituted with 4 mL of sterile water for IV injection and gently mixed to provide a solution containing 10 mg/mL of digoxin-specific antibody fragments. DigiFab should be administered slowly as an intravenous infusion over at least 30 minutes unless the patient is critically ill. Each vial of Digibind or DigiFab binds 0.5 mg of digoxin.

AVAILABILITY

Digoxin-specific antibody fragments are available as Digibind or DigiFab. Vials contain 38 mg or 40 mg of purified, lyophilized, digoxin-immune, ovine immunoglobulin fragments, respectively.

MEASUREMENT OF DIGOXIN SERUM CONCENTRATION AFTER DIGOXIN-SPECIFIC ANTIBODY FRAGMENTS ADMINISTRATION

Many laboratories are not equipped to determine free serum digoxin concentrations. Consequently, after digoxin-specific antibody fragments are administered, total serum digoxin concentrations are no longer clinically useful, because they represent free plus bound digoxin and may rise many-fold. Newer commercial methods that employ ultrafiltration or immunoassays make free digoxin measurements easier to perform and more clinically useful, but they remain associated with errors in the underestimation or overestimation of the free digoxin level.

ROLE OF DIGOXIN-SPECIFIC ANTIBODY FRAGMENTS WITH OTHER CARDIOACTIVE STEROIDS

Digoxin-specific antibody fragments were designed to have high-affinity binding for digoxin and digitoxin. There are structural similarities, however, between all cardioactive steroids. Thus, digoxin-specific antibody fragments have some efficacy in all natural cardioactive steroid poisonings, including oleander, squill, and toad venom. Dosing is entirely empiric.

63 Methylxanthines and Selective β_2-Adrenergic Agonists

The methylxanthines include caffeine, theobromine, and theophylline. Methylxanthines are used ubiquitously throughout the world, most commonly in beverages imbibed for their stimulant, mood-elevating, and fatigue-abating effects. Methylxanthines are the active ingredients in coffee (caffeine), tea (caffeine), and chocolate (theobromine), while the primary pharmaceutical is theophylline. Selective β_2-adrenergic agonists have been developed for the treatment of bronchoconstriction. Their selectivity has improved therapy for bronchoconstriction, allowing avoidance of the adverse effects of epinephrine, an α- and β-adrenergic agonist, as well as isoproterenol, a β_1- and β_2-adrenergic agonist.

EPIDEMIOLOGY

The overwhelming preponderance of caffeine consumed is in beverages; a lesser portion is consumed in foods and tablets or capsules. The use of guarana, a plant with very high caffeine content, for weight loss and athletic performance enhancement has increased dramatically in recent years. Medicinally, caffeine is used to treat neonatal apnea and bradycardia syndrome; as an analgesic adjuvant; and as an adjuvant treatment for migraine headaches, and postlumbar puncture headaches.

Theophylline, or its water-soluble salt aminophylline, is used to treat asthma and chronic obstructive pulmonary diseases. Theophylline was once the mainstay of therapy for such diseases, but more selective β_2-adrenergic agonists are now more commonly used. In neonates, theophylline and aminophylline are used similarly to caffeine to treat neonatal apnea and bradycardia syndrome.

Caffeine and theophylline toxicity result from iatrogenic as well as self-administration, and acute or chronic toxicity may occur in either circumstance. Chronic toxicity from caffeine is most typically described as a result of the frequent self-administration of caffeine. Most reported cases of theobromine poisoning occur in animals, and typically result from small animals ingesting cocoa or chocolate. Use of β_2-adrenergic agonists is also widespread. Adverse effects are associated with both therapeutic dosing and overdose. The most common toxicity results in children from unintentional ingestion of oral albuterol.

METHYLXANTHINES

Pharmacology

Methylxanthines cause the release of endogenous catecholamines, resulting in stimulation of β_1- and β_2-adrenergic receptors. Concentrations of endogenous catecholamines are extremely elevated in patients with acute methylxanthine poisoning. Methylxanthines are also adenosine antagonists, and, at supratherapeutic doses, phosphodiesterase inhibitors. Because phosphodiesterase is responsible for degradation of intracellular cyclic adenosine monophosphate (cAMP), and cAMP is the postsynaptic second messenger system of β-adrenergic stimulation, clinical effects are similar to adrenergic stimulation.

Pharmacokinetics and Toxicokinetics

Caffeine Pharmacokinetics

Caffeine is bioavailable by oral, intravenous, subcutaneous, intramuscular, and rectal routes of administration. Oral bioavailability approaches 100%. Caffeine rapidly diffuses into the total-body water and readily crosses the blood–brain barrier and the placenta. The volume of distribution is 0.6 L/kg, and 36% is protein bound. Caffeine is metabolized via the microsomal cytochrome P450 (CYP) system, primarily by the isozyme CYP1A2. Neonates demethylate caffeine, producing theophylline, and also possess the unique ability to convert theophylline to caffeine. The elimination half-life is 4.5 hours in healthy, adult, nonsmoking patients.

Caffeine Toxicokinetics

Therapeutic dosing in adults is 100–200 mg orally every 4 hours; a typical loading dose in neonates is 20 mg/kg, with daily maintenance dosing of 5 mg/kg. Based on case reports and series, lethal dosing in adults is estimated at 150–200 mg/kg, and death is associated with serum concentrations greater than 80 μg/mL.

Theophylline Pharmacokinetics

Theophylline is approximately 100% bioavailable by the oral route. Many of the available oral preparations are sustained release, designed to provide stable serum concentrations over a prolonged period of time with less frequent dosing. Peak absorption generally occurs 6–10 hours after ingestion of therapeutic doses of sustained-release theophylline pharmaceuticals. However, following overdose, the time to peak absorption may be doubled. Similar to caffeine, theophylline rapidly diffuses into the total-body water with a volume of distribution is 0.5 L/kg and 56% protein binding. Theophylline is metabolized primarily by CYP1A2. In healthy, adult, nonsmoking patients, the half-life is 4.5 hours. Infants and the elderly, as well as patients with cytochrome P450 inhibition, pregnant patients, and patients with cirrhosis, have longer half-lives than healthy children and adult nonsmoking patients.

Theophylline Toxicokinetics

Therapeutic serum concentrations of theophylline are 5–15 μg/mL. Life-threatening toxicity, including seizures, ventricular dysrhythmias, and death, are associated with serum concentrations of 80–100 μg/mL in acute overdoses, and serum concentrations of 40–60 μg/mL in chronic toxicity.

Theobromine

As is the case with the other methylxanthines, theobromine is well absorbed from the gut, and is 80% bioavailable. Theobromine has 21% protein binding, a volume of distribution of 0.62 L/kg, and a plasma half-life of 6–10 hours. Theobromine undergoes hepatic metabolism by the CYP system similarly to caffeine and theophylline.

Pathophysiology

Caffeine, theobromine, and theophylline all affect the same organ systems and cause qualitatively similar effects, although their potencies differ. The major

clinical effects at both therapeutic doses and in overdose result from adenosine antagonism, release of endogenous norepinephrine, and consequent β-adrenergic receptor stimulation and phosphodiesterase inhibition. Toxicity affects the gastrointestinal, cardiovascular, central nervous, and musculoskeletal systems, in addition to causing a constellation of metabolic derangements.

Gastrointestinal

In overdose, methylxanthines cause nausea. Most significant acute overdoses result in severe and protracted emesis. Direct effects on the medullary vomiting center and local effects on gastric acidity may contribute to gastrointestinal symptoms. This emesis is often difficult to control despite the use of potent antiemetics.

Cardiovascular

Methylxanthines are cardiac stimulants and result in positive inotropy and chronotropy. Tachydysrhythmias, especially supraventricular tachycardias (SVTs), are common in methylxanthine toxicity. Adenosine antagonism, catecholamine excess, and electrolyte disturbances, particularly hypokalemia, may be contributing factors in the development of dysrhythmias. Dysrhythmias occur more commonly and at lower serum concentrations in cases of chronic poisoning. At elevated serum concentrations, methylxanthines will result in peripheral vasodilation (probably from phosphodiesterase inhibition), causing a characteristic widened pulse pressure.

Pulmonary

Methylxanthines stimulate the CNS respiratory center, causing tachypnea and hyperpnea. Respiratory alkalosis, respiratory failure, respiratory arrest, and acute lung injury can all occur.

Neuropsychiatric

The stimulant and psychoactive properties of methylxanthines, particularly caffeine, elevate mood and improve performance of manual tasks. However, headache, anxiety, agitation, insomnia, tremor, irritability, hallucinations, and seizures may result from caffeine or theophylline poisoning. Seizures are a major complication of methylxanthine poisoning and typically are severe, recurrent, and refractory to standard treatment. Antagonism of adenosine, the endogenous neurotransmitter responsible for halting seizures, contributes to the difficulty in management.

Musculoskeletal

Methylxanthines increase intracellular calcium content and increase striated muscle contractility, secondarily decreasing muscle fatigue. They also increase muscle oxygen consumption and increase the basal metabolic rate. Tremor is common, and other manifestations of excitation include fasciculation, hypertonicity, myoclonus, and rhabdomyolysis.

Metabolic

Numerous metabolic derangements may result from acute methylxanthine toxicity. All result from excess adrenergic stimulation and subsequent increased metabolism. Severe hypokalemia, hypomagnesemia, and hypophosphatemia can be accompanied by hyperglycemia and a metabolic acidosis with increased serum lactate.

Chronic Methylxanthine Toxicity

The major difference between acute and chronic toxicity is the duration of exposure to the drug. Patients with chronic toxicity may manifest subtle signs, such as anorexia, nausea, palpitations, or emesis, although they may also present with seizures or dysrhythmias, even with theophylline concentrations in the 40–60-μg/mL range.

Caffeinism

Caffeinism is a syndrome of chronic toxicity resulting from excessive caffeine consumption. It may involve anxiety, palpitations, tremulousness, tachycardia, polyuria (diuresis), headache, and diarrhea. Patients suffering caffeinism may also experience withdrawal symptoms upon abstinence.

Caffeine Withdrawal

Caffeine induces tolerance and a withdrawal syndrome; headache, yawning, nausea, drowsiness, rhinorrhea, lethargy, irritability, nervousness, a disinclination to work, and depression may result on abstinence. Withdrawal begins 12–24 hours after cessation and lasts up to 1 week.

Diagnostic Testing

An ECG, serum electrolytes, and a serum caffeine or theophylline concentration are indicated in cases of methylxanthine toxicity. Because toxicity is dose related in acute overdose, serum concentrations of caffeine and theophylline may correlate with toxicity. Although overdose of caffeine may result in a spuriously elevated serum measurement for theophylline, the usefulness of this concentration in cases of caffeine toxicity is not demonstrated.

Serial theophylline concentrations, and to a lesser extent caffeine concentrations, may also be used to guide response to decontamination and extracorporeal drug-removal techniques. As such, concentrations should be obtained immediately and repeated every 1–2 hours until a downward trend is evident. Likewise, serum electrolytes, particularly potassium, should be monitored serially as long as the poisoned patient remains symptomatic and such values are in a range that may warrant treatment. Cardiac monitoring should continue until the patient is free of dysrhythmias other than sinus tachycardia, the patient has a decreasing serum methylxanthine concentration, and the patient is stable.

Management

General Principles and Gastrointestinal Decontamination

After ensuring adequacy of airway, breathing, and circulation, supportive care and maintenance of vital signs, decisions regarding gastrointestinal decontamination can be made. Activated charcoal is the only gastrointestinal decontamination that should be routinely considered for methylxanthine ingestion. Following severe methylxanthine overdose, however, orogastric lavage, multiple-dose activated charcoal, and/or whole-bowel irrigation should be considered where appropriate (Chap. 8).

Treatment of Gastrointestinal Toxicity

It is essential to control vomiting, as activated charcoal plays a crucial role in management. Phenothiazine antiemetics are contraindicated in methylxanthine

poisoning because they are typically ineffective and may lower the seizure threshold. Metoclopramide may be used, but a more potent serotonin (5-HT_3)-antagonist antiemetic, such as ondansetron or granisetron, may be required.

Treatment of Cardiovascular Toxicity

Hypotension should initially be treated by administration of isotonic intravenous fluid, such as 0.9% sodium chloride or lactated Ringer solution, in bolus volumes of 20 mL/kg. If an acceptable blood pressure cannot be maintained despite several fluid boluses, vasopressors should be administered. A pure α-adrenergic agonist, such as phenylephrine, is the pressor of choice in such a situation, although norepinephrine is also acceptable. When hypotension is refractory to vasopressor therapy, cautious administration of a β-adrenergic antagonist such as esmolol may be warranted. Any β-adrenergic antagonist therapy should ideally be preceded and accompanied by repeated measurement of cardiac output and vascular resistance to help guide therapy.

Administration of adenosine should not be expected to convert a methylxanthine-induced SVT. Primary treatment for SVT includes administration of benzodiazepines, which work to abate CNS stimulation and concomitant release of catecholamines. More focused pharmacologic therapy to treat SVT includes the administration of a β-adrenergic antagonist or calcium channel blocker. In the nonasthmatic patient, a β-adrenergic antagonist is preferred. However, because of the risk of provoking bronchospasm, calcium channel blockers are preferred in patients with reactive airways disease. Correction of hypokalemia and hypomagnesemia is important when ventricular dysrhythmias are present.

Treatment of Central Nervous System Toxicity

Administration of a benzodiazepine is appropriate treatment for anxiety, agitation, or seizure. Unfortunately, the seizures associated with methylxanthine toxicity are severe and often refractory to treatment. Seizures not controlled with 1 or 2 therapeutic doses of a benzodiazepine should be treated with a barbiturate or propofol. No delay should occur before administering such medications as permanent CNS injury seems more common with methylxanthine-associated seizures than with many other causes. It is important to note that phenytoin and fosphenytoin are of no benefit in controlling methylxanthine-induced seizures.

Enhanced Elimination

In cases of severe toxicity many methods of enhanced elimination can be considered. Multiple-dose activated charcoal (MDAC) therapy is essential in preventing and reversing signs and symptoms of poisoning. Charcoal hemoperfusion and hemodialysis may be effective when MDAC therapy is inadequate. Infants with methylxanthine poisoning who may be too ill, unstable, or small for other modalities can be treated with exchange transfusion.

Although charcoal hemoperfusion is the single most effective method to remove methylxanthines, the familiarity of hemodialysis and the added benefit of correction of fluid, electrolyte, and acid–base abnormalities have made hemodialysis the preferred method in many centers. Ideally, hemoperfusion and hemodialysis are performed in series. Indications for extracorporeal therapy in theophylline overdose are shown in Table 63–1. Because caffeine and theobromine concentrations are not easily obtained, therapy should be based on clinical parameters, such as the inability to take activated charcoal, seizures, and cardiovascular instability. Because it often takes hours to initiate

TABLE 63–1. Therapeutics for Methylxanthines and Selective β_2-Adrenergic Agonist Poisoning

System	Indication	Therapeutics	Comments
Cardiovascular	Hypotension	Vasopressors Phenylephrine Norepinephrine	
		β-Adrenergic antagonists	Relatively contraindicated in asthmatic patients Only with hemodynamic monitoring
	Supraventricular dysrhythmias	Calcium channel blockers	
		β-Adrenergic antagonists	Relatively contraindicated in asthmatic patients
	Ventricular dysrhythmias	Antidysrhythmics Lidocaine	
		β-Adrenergic antagonists	Relatively contraindicated in asthmatic patients
Gastrointestinal	Emesis	Antiemetics Metoclopramide Ondansetron Granisetron	
	Hematemesis	Proton pump inhibitors	
		H_2 antagonists	Cimetidine may decrease clearance of methylxanthines and prolong toxicity
CNS	Anxiety, agitation, seizure prophylaxis, seizures	Benzodiazepine, barbiturates, propofol	
Metabolic	Metabolic acidosis	Sodium bicarbonate	
	Hypokalemia	Potassium chloride	
		β-Adrenergic antagonists	Not routinely recommended for this purpose Relatively contraindicated in asthmatic patients

hemodialysis, early consultation with a nephrologist is indicated, as the goal is to prevent life-threatening toxicity, rather than respond to it.

SELECTIVE β_2-ADRENERGIC AGONISTS

Pharmacology

Selective β_2-adrenergic agonists increase intracellular cAMP. The resultant effects include relaxation of vascular, bronchial, and uterine smooth muscle, enhanced glycogenolysis in skeletal muscle, and hepatic glycogenolysis and gluconeogenesis. These drugs can be thought of as similar to the methylxanthines, but with less toxicity because of a lack of effect on adenosine and phosphodiesterase.

Pharmacokinetics

These drugs are used inhalationally, orally, and parenterally. Absorption, distribution, and elimination vary. The half-life of albuterol is approximately 4 hours.

Toxicokinetics

Ingestion of β_2-adrenergic agonists can cause significant symptomatology. For oral albuterol, 1 mg/kg appears to be the threshold for developing toxicity.

Toxicity

Gastrointestinal

Nausea and emesis are common adverse effects, but they are generally not as severe as those resulting from methylxanthine toxicity.

Cardiac

Cardiac dysrhythmias are most frequently supraventricular in origin and clinically inconsequential. Dysrhythmias other than sinus tachycardia should not be routinely attributed to β_2-adrenergic antagonist toxicity until other causes are excluded. Myocardial infarction is associated with both albuterol and isoproterenol therapy in patients with severe bronchospasm and should be expected in overdose, especially in patients with underlying cardiovascular disease.

Metabolic

Severe hypokalemia results from influx of extracellular potassium into the intracellular compartment. Other effects of β_2-adrenergic agonist poisoning include hypomagnesemia and hypophosphatemia.

Diagnostic Testing

β-Adrenergic agonist concentrations are not available in a time frame that allows for clinical decision making. As such, a determination of electrolytes and an ECG usually suffice. In many circumstances, testing is not necessary, based on the time of ingestion and clinical symptoms present.

Management

As toxicity is generally mild, and most cases of ingestion have spontaneous emesis, supportive care is usually sufficient. A single dose of activated charcoal can be given if not otherwise contraindicated. More aggressive therapy is only warranted in very unusual cases.

64 Local Anesthetics

Considering the frequency with which local anesthetics are administered, both within and outside healthcare facilities, the number of clinically significant toxic reactions is quite low and they are usually iatrogenic. Most poisonings result from inadvertent injection of a therapeutic dose into a blood vessel, repeated use of a therapeutic dose, or unintentional administration of a toxic dose. The amide local anesthetics have largely replaced the esters because of increased stability and relative absence of hypersensitivity reactions. Differences in metabolism of these drugs, however, result in a much higher likelihood of systemic toxicity. Bupivacaine, a potent and long-acting amide anesthetic, has the highest potential for cardiovascular toxicity, which can be refractory to conventional therapy.

Poisoning from topical benzocaine is relatively common because of the large number of nonprescription products available for teething and hemorrhoids and its widespread use, mostly as a spray, for topical mucosal anesthesia prior to intubation, upper endoscopy, and esophageal echocardiography. Methemoglobinemia accounts for the majority of adverse events (see below).

PHARMACOLOGY

Chemical Structure

Local anesthetics fall into one of two chemically distinct groups: amino esters and amino amides. The basic structure of all local anesthetics has three major components. A lipophilic, aromatic ring is connected by an ester or amide linkage to a short alkyl, intermediate chain that is bound to a hydrophilic tertiary (or, less commonly, secondary) amine.

Mode of Action

All local anesthetics function by reversibly binding to specific receptor proteins within the membrane-bound sodium channels of conducting tissues. Blockade of ion conductance through the sodium channel eventually leads to failure to form and propagate action potentials. The analgesic effect results from inhibiting axonal transmission of the nerve impulse in small-diameter myelinated and unmyelinated nerve fibers that carry pain and temperature sensation.

These effects also occur in other conductive tissues reliant on a sodium current in the heart and brain, and are the primary mechanism of toxicity. However, local anesthetics may interact with other cellular systems at clinically relevant concentrations. There is growing evidence that local anesthetics can directly affect many other organ systems and functions, such as the coagulation, immune, and respiratory systems, at concentrations much lower than those required to achieve sodium channel blockade. Study of these less well-described effects may help elucidate both therapeutic and toxic phenomenon that are incompletely explained.

TABLE 64–1. Pharmacologic Properties of Local Anesthetics

	pK_a	Protein Binding (%)	Relative Potency	Duration of Action	Approximate Maximum Allowable SC Dose (mg/kg)
Esters					
Chloroprocaine	9.3	Unknown	Intermediate	Short	10
Cocaine	8.7	92	Low	Medium	3
Procaine	9.1	5	Low	Short	10
Tetracaine	8.4	76	High	Long	3
Amides					
Bupivacaine	8.1	95	High	Long	2
Etidocaine	7.9	95	High	Long	4
Lidocaine	7.8	70	Low	Medium	4.5
Mepivacaine	7.9	75	Intermediate	Medium	4.5
Prilocaine	8.0	40	Intermediate	Medium	8
Ropivacaine	8.2	95	Intermediate	Long	3

Modified from Hondeghem L, Miller R: Local Anesthetics, Basic and Clinical Pharmacology, 4th ed. Stamford, Appleton and Lange, 1989, pp. 315–322; and Strichartz GR, Berde CB: Local Anesthetics. In: Miller RD, ed: Anesthesia, 4th ed. New York, Churchill Livingstone, 1994, pp. 489–521.

Physicochemical Properties

The primary determinant of the onset of action of a local anesthetic is its pK_a as it affects the drugs lipophilicity (Table 64–1). At physiologic pH (7.4) agents with a lower pK_a have relatively more uncharged molecules free to cross the nerve cell membrane, producing a faster onset of action than agents with a higher pK_a. Onset of action is also influenced by the total dose of local anesthetic administered as it affects concentration for diffusion.

Local anesthetic potency is highly correlated with lipid solubility of the drug. The degree of protein binding is correlated with the duration of action of a local anesthetic. When high blood concentrations are achieved, a higher degree of protein binding increases the risk for cardiac toxicity (see below).

PHARMACOKINETICS

A distinction must be made between local disposition (distribution and elimination) and systemic disposition. Local distribution is influenced by several factors, including spread of the local anesthetic by bulk flow, diffusion, transport via local blood vessels, and binding to local tissues. Local elimination occurs through systemic absorption and transfer into the general circulation and by local hydrolysis of amino ester anesthetics. Systemic absorption is dependent on the avidity of binding of local anesthetics to tissues near the site of injection and on local perfusion.

All local anesthetics, except cocaine, cause peripheral vasodilation by direct relaxation of vascular smooth muscle. The vasodilation enhances the vascular absorption of the local anesthetic. The addition of epinephrine (5 μg/mL or 1:200,000) to the local anesthetic solution decreases the rate of vascular absorption, thereby improving the depth and prolonging the duration of local action. Epinephrine rarely induces life-threatening systemic adverse effects in susceptible patients (eg, myocardial ischemia or infarction, hypertensive crisis).

The two classes of local anesthetics undergo metabolism by different routes (Chap. 74). The amino esters are rapidly metabolized by plasma cholinesterase to the major metabolite *para*-aminobenzoic acid (PABA). The amino amides are metabolized more slowly in the liver to a variety of metabolites unrelated to PABA. Patients with atypical or low concentrations of plasma cholinesterase are at increased risk for systemic toxicity from amino ester local anesthetics. Factors that decrease hepatic blood flow (eg, congestive heart failure) or that impair hepatic function (eg, cimetidine) increase the risk of toxic reactions to the amino amides and make management of serious reactions more difficult. Efficient skin penetration may be achieved by mixing lidocaine and prilocaine in their base forms in a 1:1 ratio (eutectic mixture of local anesthetics [EMLA]). Application for at least 45 minutes is required to achieve adequate dermal analgesia.

CLINICAL MANIFESTATIONS OF TOXICITY

Toxic Reactions

Regional Side Effects and Tissue Toxicity

All local anesthetics, at some concentration, are directly cytotoxic to nerve cells. However, in clinically relevant doses, these drugs rarely produce localized nerve damage. When nerve damage occurs, it is often attributed to the use of excessively concentrated solutions, hyperbaric solutions, the antioxidant sodium bisulfite, or to inappropriate formulation (eg, extreme pH).

Systemic Side Effects

Allergic Reactions

Allergic reactions to local anesthetics are extremely rare. Less than 1% of all adverse drug effects caused by local anesthetics are caused by true IgE-mediated allergic reactions. The amino esters are responsible for the majority of true allergic reactions. When hydrolyzed, the amino ester local anesthetics produce PABA, a known allergen. Cross-sensitivity among the amino ester anesthetics is common. Some multidose commercial preparations of amino amides may contain the preservative methylparaben, which is chemically related to PABA and is the most likely cause of the much rarer allergic reaction to amino amides. If a history of prior allergic reaction to a particular anesthetic is obtained from a patient requiring a local anesthetic, a drug from the opposite class can be chosen as there is no cross-reactivity between the amides and esters.

Methemoglobinemia

Methemoglobinemia is frequently reported as an adverse effect of topical and oropharyngeal benzocaine use, and is occasionally reported with use of lidocaine, tetracaine, or prilocaine. Most reports of methemoglobinemia associated with local anesthetics are the result of an excessive dose. When clinically indicated, affected patients with symptomatic methemoglobinemia should be treated with intravenous methylene blue (Chap. 122 and Antidotes in Brief: Methylene Blue).

Systemic Toxicity

Systemic toxicity for all local anesthetics correlates with plasma concentrations. The brain and heart are the primary target organs for systemic toxicity because of their rich perfusion, moderate tissue–blood partition coefficients, lack of diffusion limitations, and presence of cells reliant on voltage-gated sodium channels to produce an action potential. Recommendations have been published regarding maximal local anesthetic doses in an effort to minimize the risk for a systemic toxic reaction. These maximal recommended doses are developed to prevent infiltration of excessive drug not for intravascular injection.

The amino esters are rapidly hydrolyzed in the plasma and eliminated, explaining their relatively low potential for systemic toxicity. However, the amino amides have a much greater potential for producing systemic toxicity because termination of their therapeutic effect is through redistribution and slower metabolic inactivation.

Central Nervous System Toxicity

A gradually increasing blood concentration of lidocaine produces a common pattern of symptoms and signs (Fig. 64–1). In the awake patient, the initial symptoms are subjective and include tinnitus, lightheadedness, circumoral numbness, disorientation, confusion, auditory and visual disturbances, and lethargy. Subjective side effects occur at plasma concentrations of 3–6 μg/mL. Significant psychologic effects of local anesthetics have also been reported. Near-death experiences and delusions of actual death have been described as specific symptoms of local anesthetic toxicity. Objective signs then develop, which are usually excitatory, including shivering, tremors, and, ultimately, generalized tonic-clonic seizures (concentrations of 5–9 μg/mL). Seizures may occur at concentrations above 10 μg/mL, and higher concentrations produce coma, apnea, and cardiovascular collapse.

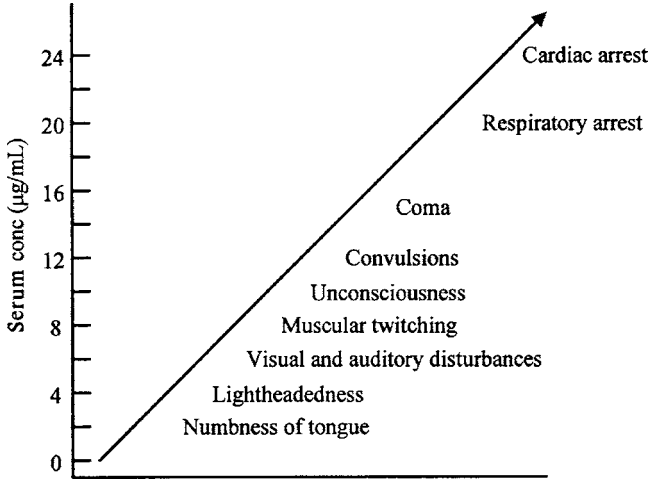


FIG. 64–1. Relationship of signs and symptoms of lidocaine toxicity to lidocaine serum concentration.

Seizures occur in patients acutely administered local anesthetics by intravenous bolus and may precede cardiac effects. Rapid intravascular injection of lidocaine may produce a brief excitatory phase, followed by generalized CNS depression with respiratory arrest. Toxicity from a large intravenous bolus of bupivacaine can even present without any CNS excitement and with bradycardia, cyanosis, and coma as the first signs.

At the first sign of possible CNS toxicity, administration of the anesthetic must be discontinued and supportive care provided. Minor symptoms usually do not require specific treatment, but should be followed closely. Although most seizures caused by local anesthetics are self-limited, they should be treated quickly if not resolving because the hypoxia and acidosis produced by prolonged convulsions may increase both CNS and cardiovascular toxicity. Barbiturates and benzodiazepines have been used for treatment of local anesthetic-induced seizures, and other standard drugs and modalities should be considered.

The cardiovascular system must be monitored closely, because when severe systemic toxicity occurs, cardiovascular depression may go unnoticed while the seizures are being treated.

Cardiovascular Toxicity

Cardiovascular (CV) side effects are the most feared manifestations of local anesthetic toxicity. Shock and CV collapse may be related to effects on vascular tone, inotropy, and dysrhythmias related to indirect CNS and direct cardiac and vascular effects of the local anesthetic. For most local anesthetics, CNS toxicity develops at a lower plasma concentration than is needed to produce cardiac toxicity; that is, have a high CV/CNS toxicity ratio. When cardiac toxicity does occur, management can be exceedingly difficult.

All local anesthetics directly produce a dose-dependent decrease in cardiac contractility, with the effects roughly proportional to their peripheral anesthetic effect. Cardiovascular toxicity of local anesthetics usually occurs following a

sudden increase in the plasma concentration, as in unintentional intravascular injection. Cardiovascular toxicity is rare in other circumstances, because a large dose of the drug is necessary to produce this effect, and also because CNS toxicity precedes CV events, thus providing a warning.

Bupivacaine is significantly more cardiotoxic than most other local anesthetics in common use. Inadvertent intravascular injection produces near simultaneous signs of CNS and cardiovascular toxicity.

LABORATORY

Serum electrolytes, blood urea nitrogen (BUN), and creatinine should be obtained to help assess the cause of cardiac dysrhythmias. Methemoglobin concentration should be obtained in patients in whom significant methemoglobinemia is clinically suspected. Rapid sensitive assays are available for measuring concentrations of lidocaine and its active monoethylglycylxylidide (MEGX) metabolite. When properly interpreted, the results of these assays can be used to avoid lidocaine toxicity, as well as to identify lidocaine toxicity in the nontherapeutic setting. Assays for determination of plasma concentrations of the other anesthetics are not routinely available. Treatment should never be delayed waiting for the results of drug concentrations.

TREATMENT

Treatment of Local Anesthetic Cardiac Toxicity

Treatment of CV complications of local anesthetics is complicated by the fact that the effects of local anesthetics on the heart are so complex. Initial therapy should focus on correcting the physiologic derangements that may potentiate the cardiac toxicity of local anesthetics, including hypoxemia, acidosis, and hyperkalemia. Cardiopulmonary resuscitation should be immediately provided and may only be necessary for a brief period while the local anesthetic redistributes from the heart. If a potentially massive intravascular local anesthetic injection is suspected, maximizing oxygenation of the patient before CV collapse occurs is critical. Despite multiple small studies suggesting efficacy of various individual pharmacologic agents, no convincing data suggest deviation from standard advanced cardiac life support (ACLS) protocols when dealing with most episodes of local anesthetic cardiac toxicity. However, the dysrhythmic effects of epinephrine are of particular concern.

Bupivacaine-induced dysrhythmias are often refractory to cardioversion, defibrillation, and pharmacologic treatment. Supportive care is all that is currently available. If the patient does not respond promptly to therapy, cardiopulmonary resuscitation can be expected to be difficult and prolonged (1–2 hours) before the depression of the cardiac conduction system spontaneously reverses as a result of redistribution and metabolism of these drugs. Cardiopulmonary bypass provides circulatory support that is far superior to closed chest cardiac massage. Hepatic blood flow is also better maintained, enhancing local anesthetic metabolism, and increased myocardial blood flow helps redistribute local anesthetics out of the myocardium. Hemodialysis is probably not useful; hemoperfusion might be useful for severe lidocaine toxicity but would be difficult to perform if significant cardiovascular depression is present. Unproved or experimental therapies include sodium bicarbonate and infusions of lipid or insulin/glucose.

65 Inhalational Anesthetics

General anesthesia occurs as a result of reversible changes in neurologic function caused by drugs that modulate synaptic neurotransmission. The commonly accepted elements of general anesthesia include hypnosis, amnesia, analgesia, inhibition of noxious reflexes, and skeletal muscle relaxation. However, precise definitions are lacking for some of these terms.

Advances in fluorine chemistry led to the cost-effective incorporation of fluorine into molecules in the development of modern anesthetics. Fluroxene was the first of the new fluorinated anesthetics to be widely used clinically. However, this anesthetic was flammable and hepatotoxic. It was largely replaced by the nonflammable halothane, which was synthesized in 1951, and introduced into clinical practice in 1956. Methoxyflurane was evaluated in humans in 1960 but is no longer used because of nephrotoxicity and hepatotoxicity. Other halogenated hydrocarbons with improved clinical properties have been introduced, including enflurane, isoflurane, desflurane, and sevoflurane. Recently, the inert gas xenon was shown to be a useful anesthetic and is currently being studied. Although environmentally friendly when compared to presently used agents, its toxicity remains relatively unknown.

PHARMACOLOGY

Because a wide range of chemically distinct compounds can produce anesthesia, it is unlikely that a unique receptor exists for inhaled anesthetics; it is more likely that the volatile anesthetics probably cause general anesthesia by modulating synaptic function from within cell membranes. The most likely targets for the inhalational anesthetics are the ion channels that control the ion flow across the cytoplasmic membrane. Many of the side effects of the inhalational anesthetics result directly from ion channel effects in nonneural tissue, primarily cardiac cell membranes.

Reversible changes in neurologic function cause loss of perception and reaction to pain, unawareness of immediate events, and loss of memory of those events.

PHARMACOKINETICS

General anesthesia works through the physicochemical behavior of volatile hydrocarbons within the hydrophobic regions of biologic membrane lipids and proteins. The potency of the various inhaled anesthetics correlates with their lipid solubility in the lipid portion of cell membranes. This mechanism is known as the *Meyer-Overton lipid-solubility theory*. Also, high pressures (100–200 atmospheres [atm]) can reverse the anesthetic effects, suggesting that anesthetics could be causing anesthesia by increasing membrane volume at normal atmospheric pressure, an effect known as the *volume expansion theory*.

Because the inhaled anesthetics enter the body through the lungs, the factors that influence their absorption by blood and distribution to other tissues include the solubility in blood, blood flow through the lungs, blood flow distribution to the various organs, solubility in tissue, and the mass of the tissue. The goal of inhalation anesthesia is to develop and maintain a satisfactory

partial pressure of anesthetic in the brain, the primary site of action. For the inhaled anesthetics, potency is commonly referred to as the minimum alveolar concentration (MAC) of the anesthetic. This is the alveolar concentration at 1 atm that prevents movement in response to a painful stimulus in 50% of subjects. MAC is used when comparing the effects of equipotent doses of anesthetics on various organ functions.

NITROUS OXIDE

Nitrous oxide is the most commonly used inhalational anesthetic in the world. Its advantages include a mild odor, absence of airway irritation, rapid induction and emergence, potent analgesia, and minimal respiratory and circulatory effects. When administered using current standards of monitoring to prevent unintentional hypoxia, it is remarkably safe. Unfortunately, nitrous oxide also has a potential for abuse, particularly among hospital and dental personnel. Death and permanent brain damage are reported, but are indirect toxic effects, secondary to hypoxia.

Deaths may rarely occur when patients receive commercially prepared nitrous oxide from tanks contaminated with impurities such as nitric oxide or nitrogen dioxide. Injury can also result from the physical properties. Because nitrous oxide is 35 times more soluble in blood than is nitrogen, any compliant air-containing space, such as bowel, will increase in size, whereas noncompliant spaces, such as the eustachian tubes, will exhibit an increase in pressure. These effects occur because nitrous oxide diffuses along the concentration gradient from the blood into a closed space much more rapidly than nitrogen can be transferred in the opposite direction. Clinical consequences include bowel distension, tympanic membrane rupture, or, more importantly, rapid progression of a pneumothorax to tension pneumothorax.

Hematologic Effects

Bone marrow depression includes leukopenia with hypoplastic bone marrow and megaloblastic erythropoiesis, which typically develops 3–5 days after initial exposure and is followed by thrombocytopenia. Recovery usually occurs within 4 days after discontinuation. The hematologic effects of exposure to nitrous oxide strongly resemble the biochemical characteristics of pernicious anemia, which results from a deficiency of vitamin B_{12}, or cyanocobalamin. Nitrous oxide oxidizes the cobalt, converting vitamin B_{12} from the active monovalent form (cob[I]alamin) to an inactive bivalent form (cob[II]alamin), resulting in both the hematologic effects and polyneuropathy.

Neurologic Effects

Disabling polyneuropathy in healthcare workers who habitually abused nitrous oxide was first described in 1978. The neurologic disorder improved slowly when the patients abstained from further nitrous oxide abuse. This neuropathy is clinically indistinguishable from subacute combined degeneration of the spinal cord associated with pernicious anemia, which is characterized by sensorimotor polyneuropathy and often combined with signs of posterior and lateral spinal cord involvement. Signs and symptoms include numbness and paresthesias in the extremities, weakness, and truncal ataxia. Neurologic changes develop only after several months of frequent exposure to nitrous oxide.

Chronic Exposure to Trace Levels of Nitrous Oxide

Dentists and dental assistants are often exposed to greater concentrations of waste anesthetic gases than individuals working in well-vented operating rooms. Epidemiologic surveys suggest a small increase in liver, kidney, and neurologic disease was found in dentists and their assistants who were chronically exposed to trace levels of nitrous oxide. For those with heavy office use of nitrous oxide, there was a 4-fold increase in the incidence of neurologic complaints as compared to the nonexposed group. Female dental assistants who were exposed to nitrous oxide also had a 2–3-fold increase in spontaneous abortion rates, reduced fertility, and a higher rate of congenital abnormalities in their offspring.

Treatment

General

Removal of the affected person from the toxic environment should be the initial intervention.

Specific

Vitamin B_{12} may help patients with a masked vitamin B_{12} deficiency who develop megaloblastic anemia and neurologic dysfunction after brief exposure to nitrous oxide, but it is not beneficial in patients who have toxicity resulting from more chronic exposure. The bone marrow abnormalities associated with nitrous oxide toxicity may be reversed by the administration of a single 30-mg, intravenous dose of folinic acid (the active form of folate) (see Antidotes in Brief: Leucovorin [Folinic Acid] and Folic Acid).

HALOGENATED HYDROCARBONS

The inhaled anesthetics were initially considered to be biochemically inert. Early reports of toxicity following their administration were poorly explained and attributed to direct effects on susceptible organs. It is now clear that the inhalational anesthetics are not inert but are metabolized in vivo, and that their metabolites are responsible for acute and chronic toxicity.

Halothane Hepatitis

Two distinct types of hepatotoxicity are associated with the use of halothane. The first is a mild dysfunction that develops in approximately 20% of exposed patients. Patients exhibit modest elevations of serum aminotransferase concentrations within a few days of anesthetic exposure. Recovery is complete. In contrast, a life-threatening hepatitis occurs in approximately 1 in 10,000 exposed patients, and produces fatal massive hepatic necrosis in 1 of 35,000 patients. This is an immunologic, rather than a strictly toxicologic, phenomenon, in which halothane or a metabolite serves as a hapten to sensitize the immune system. Factors that may increase the risk of developing hepatotoxicity from halothane include multiple exposures, obesity, female gender, age, and ethnic origin.

Enflurane, now rarely used, is weakly associated with hepatotoxicity. Isoflurane, desflurane, and sevoflurane all appear to have low hepatotoxic potential. The immune form of hepatitis is reported with all anesthetics except sevoflurane. There may be cross-sensitivity, in that prior exposure to one anesthetic may trigger hepatoxicity on exposure to a subsequent unique anesthetic.

Nephrotoxicity

Methoxyflurane causes a vasopressin-resistant polyuric renal insufficiency (nephrogenic diabetes insipidus) that lasts from 10–20 days in most patients, but occasionally longer. Renal toxicity is a result of inorganic fluoride (F^-) released during biotransformation of methoxyflurane. In the kidney, F^- may inhibit adenylate cyclase, thereby interfering with the normal action of antidiuretic hormone on the distal convoluted tubules. Methoxyflurane is no longer used, although sevoflurane may produce transient decreases in urine-concentrating ability. However, clinically evident renal impairment almost never occurs with the use of either enflurane or sevoflurane.

INHALATIONAL ANESTHETIC-RELATED CARBON MONOXIDE POISONING

Pharmacology

Desflurane, enflurane, and isoflurane contain a difluoromethoxy moiety that can be degraded to carbon monoxide (CO). This occasionally results in patient exposure to toxic CO concentrations, and in rare instances, to severe CO poisoning. The true incidence of CO exposure during clinical anesthesia is unknown and no adequate means to routinely detect intraoperative exposure exists.

Carbon monoxide production is inversely proportional to the water content of CO_2 absorbents. Soda lime and Baralyme, the two most frequently used CO_2 absorbents, are sold wet (13–15% water by weight), but wet absorbents may dry with high gas-inflow rates. Higher levels of CO are most apt to be present during the first case following a weekend because of drying of the CO_2 absorbent from a continuous inflow of dry oxygen over the weekend. If an anesthetic machine is found with the fresh-gas flow on at the beginning of the day, it is reasonable to replace the absorbent. Changing from the use of Baralyme to soda lime should also be considered as a protective measure. Clinical monitors in routine use in the operating room cannot detect CO, although more advanced monitors may do so either directly or indirectly. For example, mass spectrometry is a useful monitor for indirect detection of CO poisoning in the clinical arena.

ABUSE OF HALOGENATED VOLATILE ANESTHETICS

Fatal or life-threatening complications occur when halogenated inhalational anesthetics are used for nonanesthetic purposes (suicide attempts, mood elevation, topical treatment of herpes simplex labialis). When ingested, halothane usually produces a gastroenteritis with vomiting, followed by depression of consciousness, hypotension, shallow breathing, bradycardia with extrasystoles, and acute lung injury. Coma usually resolves within 72 hours. The diagnosis should be suspected when these features occur in a patient with the odor (sweet/fruity) of halothane on his or her breath. Supportive care, including endotracheal intubation and nasogastric lavage, should be provided with protection for potentially exposed staff. Full recovery can occur without permanent organ injury.

Intravenous injections of halothane may occur as a suicide attempt or unintentionally during induction of anesthesia. Following IV injection, coma, hypotension, and acute lung injury should be expected. The acute lung injury that develops following injection results from a direct toxic effect of high concentrations of this hydrocarbon drug on the pulmonary vascular bed.

Most reported cases of halothane abuse by inhalation involve hospital personnel. Inhalation of halothane produces a pleasurable sensation similar to that described with glue sniffing. Death may result from upper airway obstruction following loss of consciousness or from dysrhythmias.

66 Neuromuscular Blockers

Curare is the generic term for the resinous arrowhead poisons used to paralyze hunted animals. The curare alkaloids are derived from the bark of the ligneous *Strychnos* vine, and the most potent alkaloids, the toxiferines, are derived from *Strychnos toxifera*.

MECHANISM OF NEUROMUSCULAR TRANSMISSION AND BLOCK

The purpose of neuromuscular blockers (NMBs) is to reversibly inhibit transmission at the skeletal neuromuscular junction (NMJ). All NMBs possess at least one positively charged quaternary ammonium moiety that binds to the postsynaptic nicotinic acetylcholine (nACh) receptor at the NMJ, inhibiting its normal activation by acetylcholine (ACh). Activation of this receptor opens a sodium channel that leads to myocyte depolarization. Skeletal muscle paralysis can occur by several mechanisms. For example, tetrodotoxin blocks voltage-sensitive sodium channels, preventing action potential conduction by the motor neuron. Conversely, botulinum toxin blocks the release of ACh from the presynaptic neuron by inhibiting the binding of ACh-containing vesicles to the neuronal membrane in the region of the synaptic cleft. Modulation of postsynaptic ACh receptor activity at the neuromuscular junction can produce paralysis by 1 of 2 mechanisms: depolarizing (phase I block) and nondepolarizing (phase II block). Succinylcholine is the only depolarizing NMB (DNMB) in current clinical use; the other drugs discussed are all nondepolarizing NMBs (NDNMBs). Nicotine at high doses can also cause a depolarizing block.

Succinylcholine, a dimer of acetylcholine, is not hydrolyzed efficiently by junctional (true) acetylcholinesterase (AChE), and leads to a sustained local muscle endplate depolarization. In turn, this causes prolonged inactivation of the voltage-gated sodium channel, inducing a desensitization block. The muscle is temporarily refractory to presynaptic release of ACh (phase I block), which defines succinylcholine as a depolarizing neuromuscular blocker.

The NDNMBs cause skeletal muscle paralysis by competitively inhibiting the effects of ACh and thus preventing muscle depolarization. The NDNMBs are classified by duration of action as ultrashort, short, intermediate, and long. They are also classified by chemical structure as either synthetic benzylisoquinolinium drugs or as aminosteroids, which are derived from plant alkaloids.

PHARMACOKINETICS

The NMBs are highly water soluble and relatively insoluble in lipids and thus cross the blood–brain barrier (BBB) poorly. Table 66–1 presents their relevant pharmacology.

In general, small, fast-contracting muscles such as the eye are more susceptible to neuromuscular blockade than are larger, slower muscles such as the diaphragm—this is the so-called respiratory-sparing effect. Following an IV bolus of a NDNMB, paralysis of the diaphragm is coincident with paralysis of laryngeal muscles because their high perfusion results in rapid drug diffusion into the NMJ. Recovery from NMB is fastest for the diaphragm and intercostal muscles, inter-

TABLE 66–1. Pharmacology of Selected NMB Drugs

Name[a]	Class	Duration	Initial Dose (mg/kg)[b,c]	Onset (min)[d]	Clinical Duration (min)[e]	Recovery Index 25–75% (min)[f]
Succinylcholine	Depolarizer	Ultrashort	0.6–1	1–1.5	3–7	2
Atracurium	Nondepolarizer, benzylisoquinolinium	Intermediate	0.4	2–4	20–40	11
Cisatracurium		Intermediate	0.1	2–4	35–50	10–15
Doxacurium		Long	0.05	4–6	90–120	30–45
Mivacurium	Nondepolarizer, aminosteroid	Short	0.16	2–4	15–20	6–12
Tubocurarine		Long	1	4–6	60–90	48
Pancuronium		Long	0.14	3–6	60–100	55
Rocuronium		Intermediate	0.6	1.5–3	30–40	10–15
Vecuronium		Intermediate	0.1	2–4	20–40	10–15

	Renal Excretion (%)[g]	Biliary Excretion (%)[h]	Effect of Renal Failure	Effect of Hepatic Failure	Active Metabolite	Histamine Release	Effect on HR	Prolonged Block Reported
Succinylcholine	<10	Minimal	Minimal	Minimal	? Succinic acid	Minimal	(Rare) severe bradycardia	Atypical/deficient plasma AChE, phase II block
Atracurium	5–10	Minimal	No effect	Minimal to none	No, but laudanosine	Minimal	No	Yes
Cisatracurium	10–20	Minimal	No effect or minimal	No effect	No, but laudanosine	No	No	Yes
Doxacurium	50–70	Minimal	Minimal	Minimal	?	No	No	Yes
Mivacurium	<10	Minimal	Prolonged	Prolonged	No	Minimal	No	Atypical/deficient plasma AChE

Tubocurarine	40–50	10	Duration	Minimal	No	Marked	Tachycardia	No
Pancuronium	40–60	10–20	Duration drug and metabolites	Mild	3-Desacetyl-pancuronium	No	Tachycardia	Yes
Rocuronium	10–20	50–70	Minimal duration	Duration	No	No	Tachycardia at high dose	Yes
Vecuronium	20–40	40–70	Duration drug and metabolites	Duration drug and metabolites	3-Desacetyl-vecuronium	No	No	Yes

[a]Generic name (trade name, year introduced): succinylcholine (Anectine, 1951), atracurium (Tracrium, 1983), cisatracurium (Nimbex, 1995), doxacurium (Nuromax, 1991). Mivacurium (Mivacron, 1992), pancuronium (Pavulon, 1972), rocuronium (Zemuron, 1994), tubocurarine (Curare, 1942), vecuronium (Norcuron, 1984).
[b]Cisatracurium is labeled as mg of base per mL. Other drugs are labeled and packaged as mg of salt per mL.
[c]Typical initial dose is approximately $2 \times ED_{95}$(mg/kg).
[d]Onset = time from bolus to 100% block.
[e]Clinical duration = time from drug injection until 25% recovery of single twitch height.
[f]Recovery Index = time from 25% to 75% recovery of single twitch height.
[g]% Renal excretion in first 24 hours of unchanged drug.
[h]% Biliary excretion in first 24 hours of unchanged drug.
Adapted from Donati F: Neuromuscular blocking drugs for the new millennium: Current practice, future trends—Comparative pharmacology of neuromuscular blocking drugs. Anesth Analg 2000;90:S2–S6; McManus MC: Neuromuscular blockers in surgery and intensive care, part 1. Am J Health Syst Pharm 2001;58:2287–2299; Murray MJ, Cowen J, DeBlock H, et al: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 2002:30:142–156.

mediate for the large muscles of the trunk and extremities, and slowest for the adductor pollicis, larynx, pharynx, and extraocular muscles.

COMPLICATIONS OF NEUROMUSCULAR BLOCKERS

Complications associated with the use of NMBs include (a) problems associated with the care of a patient who is therapeutically paralyzed (eg, undetected hypoventilation caused by ventilator or airway problems, impaired ability to monitor neurologic function, unintentional patient awareness, peripheral nerve injury, deep vein thrombosis, and skin breakdown); (b) immediate side effects; and (c) effects occurring following prolonged drug exposure.

Patient Awareness

The NMBs do not affect consciousness and therefore a sedative must be coadministered in conscious patients. The pupillary light reflex, an important indicator of midbrain function, is preserved in healthy subjects who have received NDNMBs because pupillary function is mediated by muscarinic cholinergic receptors, for which the NMBs have no affinity.

Histamine Release

The benzylisoquinolinium NDNMBs produce direct, nonimmunologic dose- and rate-related histamine release from tissue mast cells. The approximate rank order for histamine release is tubocurarine > atracurium and mivacurium > succinylcholine.

Anaphylaxis

Of the anaphylactic reactions occurring during general anesthesia, approximately 60% are caused by NMBs, whereas only 17% are caused by latex. Rocuronium is responsible for 43% and succinylcholine for 23% of all NMB-associated anaphylaxis. Pancuronium is the drug least associated with serious allergic reactions.

Control of Respiration

At subparalyzing doses, NDNMBs blunt the hypoxic ventilatory response (HVR) but not the ventilatory response to hypercapnia. At paralyzing doses, they prevent the mechanics of ventilation.

Autonomic Side Effects

The neuronal nACh receptors found in autonomic ganglia are less susceptible to block by NMBs. Notably, tubocurarine also blocks nACh receptors at the parasympathetic ganglia, causing tachycardia, and at the sympathetic ganglia, blunting the sympathetic response.

Dysrhythmias, including bradycardia, junctional rhythms, ventricular dysrhythmias, and cardiac arrest, occur rarely after succinylcholine. This most likely results from stimulation of the cardiac muscarinic receptors and can be prevented by pretreatment with atropine.

Interactions of Muscle Relaxants with Other Drugs and Pathologic States

There are significant interactions of NMB with many medications and coexisting medical conditions (Table 66–2).

TABLE 66–2. Effect of Prior Administration of Many Drugs on Subsequent Response to Succinylcholine or Nondepolarizing Neuromuscular Blockers (NDNMBs)

Drug	Response to Succinylcholine	Response to Nondepolarizer
Aminoglycosides	Potentiates	Potentiates
Anticholinesterase, peripheral acting: neostigmine, edrophonium	Prolongs succinylcholine (except edrophonium)	Inhibits, prolongs mivacurium (except edrophonium)
Anticholinesterase, centrally acting: donepezil	Potentiates	Potentiates mivacurium
β-Adrenergic antagonist: propranolol	Potentiates in cats, effects in humans uncertain	Potentiates
β-Adrenergic antagonist: esmolol	? Mild prolongation	Slows onset of rocuronium and mivacurium
Botulinum toxin		Early potentiation, delayed resistance
Calcium channel blockers: nifedipine, verapamil	Potentiates	Potentiates
Carbamazepine	?	Inhibits, shortened duration
Dantrolene	?	Potentiates
Digitalis	More prone to cardiac dysrhythmias	Pancuronium increases catecholamines and may cause dysrhythmias
Furosemide		
<10 μg/kg	Potentiates	Potentiates
1–4 mg/kg	Inhibits	Inhibits
Glucocorticoids		Inhibits
Inhalational anesthetics: isoflurane	Potentiates	Potentiates
Lidocaine	Potentiates	Low-dose lidocaine potentiates block; high-dose lidocaine inhibits nerve terminals and blocks ACh binding site at postsynaptic membrane
Lithium carbonate	Prolongs onset and duration	Prolongs effect of pancuronium
Magnesium	Potentiates, may block fasciculations	Potentiates, may also prolong block
Nondepolarizing neuromuscular blocker: pancuronium	"Precurarization" with an NDNMB shortens the onset and decreases side effects of succinylcholine; tubocurarine decreases and pancuronium increases block duration	Chronic NDNMB induces resistance to their effect; mixing different NDNMBs may cause greater than additive effects, especially combining pancuronium with tubocuranine or metocurine

(continued)

TABLE 66–2. Effect of Prior Administration of Many Drugs on Subsequent Response to Succinylcholine or Nondepolarizing Neuromuscular Blockers (NDNMBs) *(continued)*

Drug	Response to Succinylcholine	Response to Nondepolarizer
Organic phosphorus compounds echothiophate	Potentiates	
Phenelzine (MAO inhibitor)	Prolongs	
Phenytoin		Resistant, shortened duration
Polypeptide antibiotics: polymyxin	Potentiates	Potentiates
Succinylcholine	Self-taming dose of succinylcholine may be used to limit muscular fasciculations	Tubocurarine, pancuronium, and vecuronium slightly prolonged by prior succinylcholine
Theophylline		Inhibits

PHARMACOLOGY OF DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS (SUCCINYLCHOLINE)

Succinylcholine is hydrolyzed mostly by plasma (pseudo-) cholinesterase (ChE) and to a slight extent by alkaline hydrolysis. Succinylcholine (1 mg/kg IV) usually increases cerebral blood flow, cortical electrical activity, intracranial pressure (ICP), and intraocular pressure (IOP), especially in lightly anesthetized patients.

TOXICITY OF DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS (SUCCINYLCHOLINE)

The important toxic reactions associated with succinylcholine include (a) anaphylaxis, (b) prolonged drug effect, (c) hyperkalemia, (d) acute rhabdomyolysis in patients with muscular dystrophy, (e) malignant hyperthermia (MH) in susceptible patients, (f) muscle spasms or trismus in myotonia congenita, and (g) cardiac dysrhythmias.

Prolonged Effect

The effects of succinylcholine can last for several hours if metabolism is slowed because of decreased or abnormal plasma ChE.

Hyperkalemia

Succinylcholine typically causes serum [K^+] to increase by about 0.5 mEq/L in normal individuals and in persons with renal failure. The acute hyperkalemic response to succinylcholine is exaggerated when there is a coexisting myopathy or a proliferation of extrajunctional muscle ACh receptors. This latter effect occurs in persons with denervation (head or spinal cord injury, stroke, neuropathy, prolonged use of NDNMBs), muscle pathology (direct trauma, crush or compartment syndrome, muscular dystrophy), critical illness (hemorrhagic shock, neuropathy, myopathy, prolonged immobility), thermal burn or cold injury, or sepsis lasting several days (eg, intraabdominal infections).

Rhabdomyolysis

Severe hyperkalemia rarely occurs in the absence of a clinical history that readily discloses an obvious risk factor, with one important exception. An acute or delayed onset of rhabdomyolysis, hyperkalemia, ventricular dysrhythmias, cardiac arrest, and death has been reported in apparently healthy children who were subsequently found to have a myopathy. If there is coexisting fever, muscle rigidity, hyperlactatemia, or metabolic and respiratory acidosis, the presumptive diagnosis of MH should also prompt immediate therapy with dantrolene.

Malignant Hyperthermia

Malignant hyperthermia is a heterogeneous disease that typically affects individuals who are otherwise healthy. The disorder is associated with a defect of a skeletal muscle regulatory/receptor protein. Inheritance is autosomal dominant with variable penetrance. In humans, multiple protein defects related to skeletal muscle ryanodine receptor type 1 (RYR-1, chromosome 19q13.1) are causally associated with MH, which may account for the heterogeneity of its inheritance and clinical presentation. The incidence of MH is about 1:20,000 in children and 1:50,000 in adults. Malignant hyperthermia most often occurs in the operating room shortly after initial exposure to anesthetic agents, but it may commence several hours into the course of a general anesthetic, or as long as 12 hours after surgery.

Drugs associated with precipitating an attack of MH are succinylcholine and volatile inhalational anesthetics (such as halothane). Agents that can be administered safely to individuals considered susceptible to MH include NDNMBs, nitrous oxide, propofol, ketamine, etomidate, benzodiazepines, barbiturates, opioids, and local anesthetics.

The immediate systemic manifestations of MH are a result of skeletal muscle hypermetabolism of skeletal muscle, including muscular rigidity. Futile cycling of calcium in the skeletal myocyte by sarcoplasmic Ca^{2+}-adenosine triphosphatase (ATPase) causes depletion of cellular adenosine triphosphate (ATP), excess heat production, core hyperthermia, increased O_2 consumption and CO_2 production, venous O_2 desaturation and hypercarbia, anaerobic metabolism, and lactic acid generation. The earliest signs of MH include an early and rapid increase in CO_2 production and arterial, venous, and end-tidal CO_2; tachycardia; tachypnea; hypertension or labile blood pressure; and skeletal and jaw muscle rigidity. Despite the name of the syndrome, hyperthermia is not a universal finding in MH. Acute potassium release from muscle cells may result in life-threatening hyperkalemia.

By partially blocking the release of calcium from skeletal muscle sarcoplasmic reticulum, dantrolene rapidly reverses the signs and symptoms of hypermetabolism (see Antidotes in Brief: Dantrolene Sodium). Calcium channel antagonists must *not* be given with dantrolene, as they can precipitate hyperkalemia and severe hypotension (Table 66–3).

Muscle Spasms

Masseter muscle rigidity (MMR) is observed in 0.3–1% of pediatric patients induced with succinylcholine and halothane. It is clinically significant because it may complicate airway management, as well as herald the onset of MH.

PHARMACOLOGY OF NONDEPOLARIZING NEUROMUSCULAR BLOCKERS

Table 66–1 details the pharmacology and toxicity of these drugs.

TABLE 66–3. Suggested Therapy for Malignant Hyperthermia

Acute-Phase Treatment of Malignant Hyperthermia (MH)

1. **Call for help.** Immediately summon experienced help when MH is suspected.
2. **Stop triggering agents,** including volatile inhalational anesthetics and succinylcholine.
3. **Hyperventilate with 100% O_2.**
4. **Administer dantrolene sodium.** Give the initial bolus of 2.5 mg/kg rapidly, followed by additional boluses until signs of MH are controlled (tachycardia, rigidity, increased end-tidal CO_2, hyperthermia). Typically, total dose of 10 mg/kg controls symptoms, but occasionally up to 3 times this dose may be required.
5. **Monitor core temperature closely.** Excessive treatment may lead to hypothermia.
6. **Actively cool the hyperthermic patient,** simultaneously with the above.
   - Immersion in ice-water slurry is best. Peritoneal or gastric lavage can also be useful.
   - Surface cool with ice and hypothermia blanket.
7. **Aggressively treat hyperkalemia.** Hyperkalemia is common and should be treated with hyperventilation, sodium bicarbonate, intravenous dextrose, and insulin. Severe hyperkalemia can also be treated with calcium administration. Hypokalemia should be treated with great caution because hyperkalemia may occur due to rhabdomyolysis.
8. **Monitor end-tidal CO_2,** arterial and mixed venous blood gases, serum potassium and calcium, PT/PTT and urine output.
9. Administer sodium bicarbonate to correct metabolic acidosis as guided by the arterial blood gas.
10. Dysrhythmias usually respond to dantrolene and correction of acidosis and hyperkalemia. If dysrhythmias persist or are life-threatening, standard antidysrhythmics can be used.
    - **Calcium channel blockers should *not* be used (especially verapamil)** to treat dysrhythmias because they can cause hyperkalemia and cardiovascular collapse.
11. Ensure adequate urine output by hydration and/or administration of mannitol of furosemide. Consider central venous or PA monitoring.
12. **For emergency consultation to help with patient management (http://www.mhaus.org/hotline.html) call the MH Emergency Hotline:**
    - Inside United States or Canada call: **800-MH-HYPER (800-644-9737)**
    - Outside the United States and Canada call: **001 315-464-7079**

Postacute-Phase Treatment of Malignant Hyperthermia

1. **Observe the patient in an ICU setting for at least 24–48 hours** because recrudescence of MH occurs in 25% of cases, particularly following a fulminant case resistant to treatment.
2. **Administer dantrolene 1 mg/kg IV q4–6h for 24–48 hours after the episode.**
3. Follow arterial blood gases, creatine phosphokinase, potassium, calcium, phosphorus, urine and serum myoglobin, PT, PTT, platelet count, and core body temperature until they return to normal values (eg, q6h). Central temperature (eg, rectal, esophageal) should be monitored continuously.
4. Counsel the patient and family regarding MH and further precautions.
   - For nonemergency patient referrals, contact MHAUS: 888-274-7899, 11 East State Street, PO Box 1069, Sherburne, NY 13460.

(continued)

TABLE 66–3. Suggested Therapy for Malignant Hyperthermia *(continued)*

- Report patients who have had an acute MH episode to the **North American MH Registry of MHAUS: 412-692-5464.**
- Alert family members to the possible dangers of MH and anesthesia.

5. Recommend an MH medical ID for the patient and have the individual wear it at all times.

Notes:

1. Each vial of dantrolene contains 20 mg of dantrolene and 3 g mannitol (to improve water solubility). Each vial should be reconstituted with 50 mL of sterile water for injection. Dissolution of the lyophilized solution in water is slow and requires thorough mixing.
2. The guideline above may not apply to every patient and of necessity must be altered according to specific patient needs.
3. Sudden unexpected cardiac arrest in children: Children younger than about 10 years who experience sudden cardiac arrest after succinylcholine in the absence of hypoxemia and anesthetic overdose should be treated for acute hyperkalemia first. In this situation, calcium chloride should be administered along with other means to reduce serum potassium. They should be presumed to have subclinical muscular dystrophy, and a neurologist should be consulted.

Atracurium is comprised of 10 different isomers, each with its unique pharmacokinetic and pharmacodynamic profile, whereas cisatracurium contains only the 1R-*cis* 1R-*cis* isomers.

TOXICITY OF NONDEPOLARIZING NEUROMUSCULAR BLOCKERS

The most important toxic effects of the NDNMB are accumulation of laudanosine, a metabolite of atracurium, and persistent weakness. In general, limiting the dose of drug and monitoring its effect with a portable nerve stimulator reduce the incidence of prolonged weakness.

Laudanosine

In the CNS, laudanosine has an inhibitory effect at the γ-aminobutyric acid, nACh, and opioid receptors that at high plasma concentrations causes neuroexcitation.

Persistent Weakness Associated with Nondepolarizing Neuromuscular Blockers

When administered for more than 48 hours, there is a risk that muscle weakness will persist longer than otherwise anticipated based on the kinetics of NDNMB elimination.

PHARMACOLOGY OF REVERSAL DRUGS

Termination of the NMB effect is initially a result of drug redistribution and subsequently by drug elimination, metabolism, and/or chemical antagonism. Pharmacologic antagonism of a partial NDNMB is achieved by giving a reversal drug that inhibits junctional AChE and increases ACh at the NMJ. This increase in ACh can overcome the competitive inhibition caused by the residual NDNMB. The commonly used anti-ChEs are polar molecules possessing a quaternary ammonium such as neostigmine or pyridostigmine. The most common and troublesome clinical side effect of ChE inhibition is bradycar-

dia, which is usually prevented by coadministration of an antimuscarinic drug such as atropine or scopolamine.

DIAGNOSTIC TESTING

Quantitative methods employing high-performance liquid chromatography and mass spectrometry are available for analysis of blood and tissue NMB (both NDNMB and succinylcholine) and metabolite concentrations.

Dantrolene Sodium

Dantrolene is an intracellular muscle relaxant; as such, it is the only drug proven to be effective for treatment and prophylaxis of human malignant hyperthermia (MH). Although it is a hydantoin derivative, structurally similar to local anesthetics and anticonvulsants, it possesses none of their properties.

PHARMACOKINETICS

Dantrolene is lipophilic and relatively insoluble in water. The drug is metabolized in the liver by hydroxylation of the hydantoin ring or by reduction of the nitro group. Up to 25% of administered dantrolene is excreted in the urine as the 5-hydroxydantrolene metabolite, which is about half as potent as the parent drug. The elimination half-life is 4–8 hours for dantrolene itself and 15 hours for its primary metabolite. Dantrolene exhibits variable absorption by the small intestine and peak blood concentrations are achieved 3–6 hours after ingestion. Oral bioavailability can be as high as 70%.

MECHANISM

Dantrolene acts at the skeletal muscle ryanodine receptor (RYR-1) causing dose-dependent inhibition of both steady-state and peak components of sarcoplasmic calcium release, reducing free myoplasmic calcium, thereby directly inhibiting excitation–contraction coupling.

INDICATIONS

Dantrolene is indicated for treatment of the fulminant skeletal muscle hypermetabolism characteristic of MH and for treatment following an acute episode of MH to prevent recrudescence. Long-term oral dantrolene therapy is used rarely to treat chronic spasticity.

Dantrolene should be considered for patients with severe hyperthermia, when the diagnosis of MH cannot be excluded with certainty, especially in the presence of a known trigger such as succinylcholine. Atypical presentations of MH in the presence or absence of triggering anesthetics have been reported.

One important caveat: if dantrolene is given for hyperthermic disorders, it is not a substitute for aggressive cooling. In heat stroke, for example, the lowering of body temperature by active cooling alone is not accelerated when dantrolene is added.

There are reports of the use of dantrolene to treat acute hyperthermia of other etiologies including neuroleptic malignant syndrome, serotonin syndrome, heat stroke, monoamine oxidase (MAO) inhibitor overdose, methylenedioxymethamphetamine (“ecstasy”) overdose, intrathecal baclofen withdrawal, and thyroid storm. There is only anecdotal support for these indications, and scientifically rigorous proof that any of these syndromes benefit from dantrolene therapy is lacking.

DOSING

Dantrolene is supplied as a sterile lyophilized solution in a 70-mL vial that contains 20 mg of dantrolene sodium and 3 g of mannitol; following reconsti-

tution with 60 mL of sterile water for injection, it has a pH of about 9.5. The vial should be vigorously shaken until the solution is clear. The initial dose of dantrolene for treatment of acute MH is a 2.5 mg/kg IV bolus; it is repeated every 15 minutes until the signs of hypermetabolism are reversed, or until a total dose of about 10 mg/kg has been administered. Occasionally higher doses are required. Following initial treatment, at least 1–2 mg/kg IV should be given every 6 hours for 1–3 days to prevent recrudescence of the syndrome. Initial dosing should probably be according to total body weight as dantrolene is lipophilic; however, its pharmacokinetics in obesity have not been determined. The key point is that the total dose of dantrolene is determined by titration to a metabolic end point—resolution of skeletal muscle hypermetabolism. When an effective dose of dantrolene is given, signs of muscle hypermetabolism start to normalize within 30 minutes.

SIDE EFFECTS AND TOXICITY

Following dilution, dantrolene has an alkaline pH and can cause venous irritation and thrombophlebitis. There is no evidence of allergic cross-reactivity with dantrolene in patients with prior phenytoin allergy.

When used in combination, dantrolene and verapamil can cause hyperkalemia and decreased cardiac output; consequently, these drugs should not be combined. The mechanism of this interaction is unclear.

When given to healthy persons or for MH prophylaxis, dantrolene can cause subjective skeletal muscle and diaphragm weakness (experienced as dyspnea), but not muscle paralysis.

67 Antipsychotics

HISTORY AND EPIDEMIOLOGY

Prior to the introduction of chlorpromazine in 1950, patients with schizophrenia were treated with nonspecific sedatives such as barbiturates. The advent of the antipsychotics in the 1950s revolutionized the care of these patients. However, it became apparent that these drugs were potentially dangerous in overdose (a common occurrence in mentally ill patients), and that they caused a host of adverse drugs effects. The latter included the extrapyramidal syndromes (EPSs), a constellation of disorders that were relatively common, sometimes irreversible, and occasionally life-threatening.

Most antipsychotic drug toxicity occurs by one of two mechanisms. Following overdose, toxicity is dose-related and reflects an extension of the effects of the drug on neurotransmitter systems and other biologic processes. In the absence of overdose, idiosyncratic toxicity can also occur.

The low-potency, typical antipsychotics such as thioridazine, but also chlorpromazine and mesoridazine are associated with greater toxicity than other antipsychotic drugs. Available data suggest a changing pattern of antipsychotic overdose that seems to reflect prescribing practices. Currently the atypical antipsychotics are more frequently implicated than the phenothiazines.

PHARMACOLOGY, PHARMACOKINETICS, AND TOXICOKINETICS

Antipsychotics can be classified in a variety of ways, according to their chemical structure, their receptor binding profiles, or as *typical* or *atypical* antipsychotics. The most widely used classification system categorizes antipsychotics as either typical or atypical. Typical antipsychotics are categorized according to their affinity for the D_2 receptor as either low potency, as exemplified by thioridazine and chlorpromazine, or high potency, as exemplified by haloperidol. They are associated with acute, subacute, and long-term motor disturbances, collectively referred to as EPSs. Most atypical antipsychotics inhibit the action of serotonin at the 5-HT_{2A} receptor and are less prone to produce EPSs. Tables 67–1 and 67–2 summarize the pharmacology of antipsychotics.

Most antipsychotics are substrates for the various isozymes of the hepatic cytochrome P450 (CYP) enzyme system. Genetic polymorphisms appear to influence the tolerability and efficacy of treatment with these antipsychotics during therapeutic use, but are unlikely to alter the severity of antipsychotic overdose. Drug interactions with xenobiotics that inhibit these enzymes increase the risk of adverse effects.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Table 67–3 shows the typical adverse effects of antipsychotics that occur with therapeutic dosing. Table 67–4 compares the extrapyramidal syndromes. The

TABLE 67–1. Commonly Used Antipsychotics

Compound	Usual Daily Adult Dose (mg)	Volume of Distribution (L/kg)	Half-Life (Range, h)	Protein Binding (%)
Typical Antipsychotics				
Droperidol	1.25–30	2–3	2–10	85–90
Haloperidol	1–20	18–30	14–41	90
Pimozide	1–20	11–62	28–214	99
Chlorpromazine	100–800	10–35	18–30	98
Promazine	50–1000	30–40	8–12	98
Promethazine	25–150	9–25	9–16	93
Fluphenazine	0.5–20	220	13–58[b]	99
Perphenazine	8–64	10–35	8–12	>90
Prochlorperazine	10–150	13–32	17–27	>90
Trifluoperazine	4–50	NR	7–18	>90
Mesoridazine	100–400	3–6	2–9	98
Thioridazine	200–800	18	26–36	96
Chlorprothixene	30–300	11–23	8–12	NR
Flupentixol	3–6	7–8	7–36	NR
Thiothixene	5–30	NR	12–36	>90
Atypical Antipsychotics				
Amisulpride	50–1200	5.8	12	16
Raclopride	3–6	1.5	12–24	NR
Remoxipride	150–600	0.7	3–7	80
Sulpride	200–1200	0.6–2.7	4–11	14–40
Clozapine	50–900	5.4 ± 3.5	6–17	95
Loxapine[a]	20–250	NR	2–8	90–99
Olanzapine	5–20	10–20	21–54	93
Quetiapine	150–750	10	3–9	83
Risperidone	2–16	0.7–2.1	3–20	90
Sertindole	12–24	20–40	24–200	99
Ziprasidone	40–160	2	4–10	99
Aripiprazole	10–30	5	47–68	99

NR = not reported.
[a]Loxapine's atypical profile is lost at doses >50 mg/d; hence it is sometimes categorized as a typical antipsychotic.
[b]For hydrochloride salt; enanthate and decanoate have ranges of 3–4 days and 5–12 days, respectively.

incidence of EPSs appears to be highest with the more potent antipsychotics such as haloperidol, and lower with the less potent antipsychotics chlorpromazine and thioridazine. Atypical antipsychotics are associated with an even lower incidence of EPS.

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening neurologic emergency. Although NMS most often occurs during treatment with a D_2-receptor antagonist, withdrawal of dopamine agonists can produce an indistinguishable syndrome. Postulated risk factors for the development of NMS include young age, male gender, extracellular fluid volume contraction, use of high-potency antipsychotics, depot preparations, cotreatment with lithium, multiple agents in combination, and rapid dose escalation. The pathophysiology of NMS is incompletely understood but appears to involve abrupt reductions in central dopaminergic

TABLE 67–2. Toxic Manifestations of Selected Antipsychotics

	α_1-Adrenergic Antagonism	Muscarinic Antagonism	Fast Sodium Channel (I_{Na}) Blockade	Delayed Rectifier (I_{Kr}) Current Blockade
Clinical effect	Hypotension	Central and peripheral anticholinergic effects	QRS widening; rightward T40 msec; myocardial depression	QTc prolongation; torsades de pointes
Typical agents				
Chlorpromazine	+ + +	+ +	+ +	+ +
Fluphenazine	–	–	+	+
Haloperidol	–	–	+	+ +
Loxapine	+ + +	+ +	+ +	+
Mesoridazine	+ + +	+ + +	+ + +	+ +
Perphenazine	+	–	+	+ +
Pimozide	+	–	+	+ +
Thioridazine	+ + +	+ + +	+ + +	+ + +
Trifluoperazine	+	–	+	+ +
Atypical agents				
Aripiprazole	+ +	–	–	–
Clozapine	+ + +	+ + +	–	+
Olanzapine	+ +	+ + +	–	–
Quetiapine	+ + +	+ + +	+	– to +
Remoxipride	–	–	–	–
Risperidone	+ +	–	–	–
Sertindole	+	–	–	+ +
Ziprasidone	+ +	–	–	+ + +

TABLE 67–3. Adverse Effects of Antipsychotics

CNS	Somnolence, coma
	Respiratory depression or loss of airway reflexes
	Hyperthermia
	Seizures
	Extrapyramidal syndromes
	Central anticholinergic syndrome
Cardiovascular	
Clinical	Tachycardia
	Hypotension (orthostatic or resting)
	Myocardial depression
Electrocardiographic	QRS complex widening
	Right deviation of terminal 40 msec of frontal plane axis
	QTc prolongation
	Torsades de pointes
	Nonspecific repolarization changes
Endocrine	Amenorrhea, oligomenorrhea, or metrorrhagia
	Breast tenderness and galactorrhea
Gastrointestinal	Impaired peristalsis
	Dry mouth
Genitourinary	Urinary retention
	Ejaculatory dysfunction
	Priapism
Ophthalmic	Mydriasis or miosis
	Visual blurring
Dermatologic	Impaired sweat production
	Cutaneous vasodilation

neurotransmission in the hypothalamus, altering the core temperature "set point" and leading to altered thermoregulation and other manifestations of autonomic dysfunction. Blockade of striatal D_2 receptors contributes to muscle rigidity and tremor. Table 67–5 summarizes the clinical effects of NMS.

The provision of good supportive care is the cornerstone of treatment for NMS. It is essential to recognize the condition as an emergency and withdraw the offending agent immediately. When NMS ensues following the abrupt discontinuation of a dopamine agonist such as levodopa, the drug should be reinstituted promptly. Most patients with NMS should be admitted to an intensive care unit. Supplemental oxygen should be administered, and assisted ventilation may be necessary in cases of respiratory failure, which can result from central hypoventilation, loss of protective airway reflexes, or rigidity of the muscles of the chest wall.

For patients with life-threatening hyperthermia, submersion in an ice water bath is the most rapidly efficient technique (Chap. 16). In patients with less severe illness, evaporative cooling can be accomplished by the removal of the patient's clothing, spraying with lukewarm water, and maintaining constant air circulation with the use of fans. Hypotension should be treated initially with large volumes of 0.9% sodium chloride solution, followed by vasopressors, if necessary. Alkalinization of the urine with sodium bicarbonate may reduce the incidence of myoglobinuric renal failure in patients with high creatine kinase concentratons, but maintenance of euvolemia and adequate renal

TABLE 67–4. The Extrapyramidal Syndromes

Disorder	Time of Maximal Risk	Features	Postulated Mechanism	Possible Treatments
Acute dystonia	Hours to a few days	Sustained, involuntary muscle contraction, torticollis, including blepharospasm, oculogyric crisis	Imbalance of dopaminergic/cholinergic transmission	Anticholinergics, benzodiazepines
Akathisia	Hours to days	Restlessness and uneasiness, inability to sit still	Mesocortical D_2 antagonism (?)	Dose reduction, trial of alternate drug, propranolol, benzodiazepines, anticholinergics
Parkinsonism	Weeks	Bradykinesia, rigidity, shuffling gait, masklike facies, resting tremor	Postsynaptic striatal D_2 antagonism	Dose reduction, anticholinergics, dopamine agonists
Neuroleptic malignant syndrome	2–10 days	Many (see Table 67–5): altered mental status, motor symptoms, hyperthermia, autonomic instability	D_2 antagonism in striatum, hypothalamus, and mesocortex	Cooling, benzodiazepines, supportive care, consider bromocriptine, dantrolene, amantadine
Tardive dyskinesia	3 months to years	Late-onset involuntary choreiform movements, buccolinguomasticatory movements	Excess dopaminergic activity	Recognize early and stop offending drug; addition of other antipsychotic; cholinergics

Data from Pierre JM: Extrapyramidal symptoms with atypical antipsychotics: Incidence, prevention and management. Drug Saf 2005;3:191–208; and Trosch RM: Neuroleptic-induced movement disorders: Deconstructing extrapyramidal symptoms. J Am Geriatr Soc 2004;12(Suppl):S266–S271.

TABLE 67–5. Clinical and Laboratory Features of the Neuroleptic Malignant Syndrome

Feature	Potential Manifestations
Altered mental status	Delirium, lethargy, confusion, stupor, catatonia, coma
Motor symptoms	"Lead pipe" rigidity, cogwheeling, dysarthria or mutism, parkinsonian syndrome, akinesia, tremor, mutism, dystonic posture, dysphagia, dysphonia, choreiform movements
Hyperthermia	Temperature >100.4°F (38°C)
Autonomic instability	Tachycardia, diaphoresis, sialorrhea, incontinence, respiratory irregularities, cardiac dysrhythmias, hypertension, or hypotension
Laboratory findings	Increased muscle enzymes (creatine kinase, lactate dehydrogenase, aldolase), leukocytosis, renal insufficiency (reflecting volume contraction and pigment nephropathy), acidemia, myoglobinuria, modest aminotransferase elevation, hypoxia, hyponatremia, increased prothrombin time/partial thromboplastin time

These manifestations can occur in any combination, although hyperthermia and some degree of increased muscular activity usually are present. Some manifestations may be fleeting. A supportive medication history is essential to the diagnosis, and every effort should be made to exclude other potential causes, such as other medical illnesses and other drugs and toxins.

perfusion is of greater importance. Venous thromboembolism is a major cause of morbidity and mortality in patients with NMS, and anticoagulant prophylactic therapy should be considered in patients likely to be immobilized for more than 12–24 hours.

Benzodiazepines are considered first-line therapy in patients with NMS. Benzodiazepines should be dosed incrementally to induce muscle relaxation and sedation. Dantrolene and bromocriptine are not well studied and their incremental benefit over good supportive care is debated. However, these drugs are associated with relatively little toxicity, and the absence of definitive evidence should not preclude their use. Bromocriptine is a centrally acting dopamine agonist given orally or by nasogastric tube at doses of 2.5–10 mg 3–4 times daily. Dantrolene is given by intravenous infusion (2.5 mg/kg up to 10 mg/kg/d in severe cases). When these drugs are used, they should be tapered slowly after the patient improves so as to minimize the likelihood of recrudescent NMS.

Acute Overdose

Antipsychotic overdose can produce a spectrum of toxic manifestations affecting multiple organ systems, but most serious toxicity involves the CNS and cardiovascular system. Impaired consciousness is a common and dose-dependent feature of antipsychotic overdose, ranging from somnolence to frank coma. Although this may be associated with impaired airway reflexes, significant respiratory depression is uncommon. Many antipsychotics are potent muscarinic antagonists and can produce an anticholinergic syndrome. Peripheral manifestations include tachycardia, decreased production of sweat and saliva, flushed skin, urinary retention, diminished bowel sounds, and mydriasis, although miosis also occurs. Mild elevations in body temperature are common and reflect impaired heat dissipation as a consequence of impaired

sweating, as well as increased heat production in agitated patients. Tachycardia reflects both anticholinergic effects and a compensatory response to arterial hypotension. Hypotension results from peripheral α_1-adrenergic blockade, which reduces vasomotor tone.

The electrocardiographic (ECG) manifestations of antipsychotic overdose are similar to those of tricyclic antidepressant (TCA) toxicity (Chaps. 5 and 71) and include widening of the QRS complex, and a rightward deflection of the terminal 40 msec of the QRS complex. Prolongation of the QTc results and creates a substrate for the development of torsades de pointes.

DIAGNOSTIC TESTS

The diagnosis of antipsychotic poisoning is supported by the clinical history, the physical examination, and a limited number of adjunctive tests. Both the clinical and ECG findings described above are nonspecific and can occur following overdose of several different drug classes, including TCAs, skeletal muscle relaxants, carbamazepine, and first-generation antihistamines. Moreover, the absence of typical ECG changes does not exclude a significant antipsychotic ingestion. Plasma concentrations of antipsychotics are not widely available, do not correlate well with clinical signs and symptoms, and do not help guide therapy. Qualitative urine drug screens may confirm the presence of antipsychotics, but are of little prognostic value. Blood and urine immunoassays for TCAs may yield a false positive in the presence of phenothiazines.

MANAGEMENT

Other drugs, particularly other psychotropics, may have been coingested and can confound both the clinical presentation and management. Regularly encountered coingestants include antidepressants, sedative-hypnotics, anticholinergics, valproic acid, and lithium, as well as ethanol and nonprescription analgesics such as acetaminophen and aspirin. Supportive care is the cornerstone of treatment for patients with antipsychotic overdose. Supplemental oxygen should be administered if hypoxia is present, and patients with altered mental status should receive thiamine, naloxone, and parenteral dextrose as needed. Intubation and ventilation are rarely required, but may be necessary for patients with very large overdoses of antipsychotics or ingestion of other CNS depressants. All symptomatic patients should have continuous cardiac monitoring, reliable venous access, and an electrocardiogram.

Asymptomatic patients with normal ECGs 6 hours following exposure are at exceedingly low risk of complications and no longer require cardiac monitoring. Symptomatic patients and those with abnormal ECGs should have continuous monitoring for a minimum of 24 hours.

Gastrointestinal Decontamination

Gastrointestinal decontamination with activated charcoal (1 g/kg by mouth or nasogastric tube) should be considered for patients who present within a few hours of a large or polydrug overdose. Induced emesis is absolutely contraindicated because of the high potential for pulmonary aspiration. Orogastric lavage and whole-bowel irrigation are unlikely to be necessary in the absence of coingestants.

Treatment of Cardiovascular Complications

Vital signs should be monitored closely. Hypotension should be treated initially with the appropriate titration of 0.9% sodium chloride solution. If vasopressors are required, direct-acting α agonists, such as norepinephrine or phenylephrine, are preferred over dopamine, which is an indirect agonist and is likely to be ineffective.

Progressive widening of the QRS complex reflects sodium channel blockade and may be associated with reduced cardiac output and malignant ventricular dysrhythmias. Sodium bicarbonate (1–2 mEq/kg) is the first-line therapy for ventricular dysrhythmias and should be considered for patients with dysrhythmias or QRS widening of >0.10 seconds (see Antidotes in Brief: Sodium Bicarbonate and Chap. 71). Repeated doses of bicarbonate can be given to achieve a target blood pH of 7.5. If the patient is intubated, hyperventilation may also be employed but it is not comparably efficacious. If ventricular dysrhythmias persist despite sodium bicarbonate, lidocaine (1–2 mg/kg followed by continuous infusion) is a reasonable second-line antidysrhythmic. Class IA and IC antidysrhythmics (procainamide, disopyramide, quinidine, propafenone, encainide, and flecainide), and class III antidysrhythmics (amiodarone, sotalol, and bretylium) can aggravate cardiotoxicity and should not be used.

Prolongation of the QTc requires no specific treatment other than the correction of potential contributing causes such as hypokalemia and hypomagnesemia. Torsades de pointes should be treated with intravenous magnesium sulfate, using care to avoid hypotension, which is dose- and rate-dependent. Overdrive pacing with isoproterenol, transcutaneous or transvenous pacing should be considered if magnesium sulfate fails, although in theory this may worsen the rate-dependent sodium channel blockade.

Treatment of Seizures

Seizures are generally short-lived and often require no pharmacologic treatment. Multiple or refractory seizures can be treated with benzodiazepines. Although secondary anticonvulsants are rarely necessary, refractory seizures should respond to propofol infusion or general anesthesia.

Treatment of the Central Antimuscarinic Syndrome

Case reports and observational studies suggest that physostigmine (see Antidotes in Brief: Physostigmine Salicylate) can safely and effectively ameliorate the agitated delirium associated with the central anticholinergic syndrome. Physostigmine should be used with caution, and avoided in patients with dysrhythmias, any degree of heart block, or widening of the QRS complex. If physostigmine is used, it should be given as 1–2 mg over 3–5 minutes, and the patient should be observed closely (see Antidotes in Brief: Physostigimine). If bradycardia, bronchospasm, or bronchorrhea develop, they can be treated with atropine or glycopyrrolate. The effects of physostigmine are transient, typically ranging from 30–90 minutes, and additional doses are often necessary.

Enhanced Elimination

There is no pharmacologic rationale to support the use of multiple-dose charcoal or manipulation of urinary pH to increase the clearance of antipsychotics. Because most antipsychotics have large volumes of distribution and extensive protein binding, neither hemodialysis nor hemoperfusion are expected to significantly increase their clearance.

68 Lithium

Lithium is one of the most efficient long-term therapies and preventive treatments for bipolar affective disorders with a demonstrated antisuicidal effect, and an ability to improve both the manic and depressive symptoms of this illness. In most industrialized nations, approximately 1 person in 1000 is using one or more of the various formulations of lithium.

PHARMACOLOGY

The simplicity of the lithium molecule belies the complexity of its mechanism of action, which is currently not fully clarified. Lithium has effects on serotonin release and receptor sensitivity and modulates the effect of norepinephrine. However, the substantial delay to therapeutic effect makes it unlikely that the mechanism of action is solely caused by acute biochemical interactions. There has been a recent focus on altered cellular signaling, neuronal plasticity, and neurogenesis. The current prevailing theory of the mechanism of action of lithium centers around inositol depletion.

PHARMACOKINETICS AND TOXICOKINETICS

The volume of distribution of lithium is between 0.6 and 0.9 L/kg. It displays no discernible protein binding, and distributes freely in total body water, except for the cerebrospinal fluid (CSF), from which it is actively extruded. The immediate-release preparations of lithium are rapidly absorbed from the GI tract. Peak serum concentrations are achieved within 1–2 hours. Sustained-release products demonstrate variable absorption, with a delay of 6–12 hours, and in overdose there may be a longer delay to reach peak concentrations or there may be multiple peaks. There is a significant delay in reaching a steady state, and lithium distribution into the brain can take up to 24 hours to reach equilibrium. Chronic therapy prolongs the elimination of lithium, as does advancing age.

Each 300-mg lithium carbonate tablet contains 8.12 mEq of lithium. Ingestion of a single 300-mg tablet would be expected to raise the serum lithium concentration by approximately 0.1–0.3 mEq/L (assuming a patient weight of 50–100 kg).

Lithium is eliminated almost entirely (95%) by the kidneys, with a small amount eliminated in the feces. In an adult with normal renal function, lithium clearance ranges from 25–35 mL/min. Lithium is handled by the kidneys much in the same way as sodium. Lithium is freely filtered, and more than 60% is reabsorbed by the proximal tubule. Any condition that makes the kidney sodium avid, such as volume depletion or salt restriction, increases the reabsorption of lithium in the proximal tubule. Risk factors for the development of lithium toxicity therefore include advanced age with its decrease in glomerular filtration rate (GFR), thiazide diuretics, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, decreased sodium intake, and low-output heart failure.

The therapeutic index for lithium is narrow. The generally accepted steady-state therapeutic range of plasma lithium concentrations is 0.6–1.2 mEq/L.

CLINICAL MANIFESTATIONS

In acute lithium toxicity, the patient has no body burden of lithium present at the time of ingestion. The toxicity that develops depends on the rate of ab-

sorption and distribution. In chronic toxicity, the patient has a stable body burden of lithium with the serum concentration maintained in the therapeutic range, and then some factor disturbs this balance, either by enhancing absorption, or more commonly, decreasing elimination. For the chronic user of lithium, small perturbations in the equilibrium between intake and elimination can lead to toxicity. In acute-on-chronic toxicity, the patient ingests an increased amount of lithium (intentionally or unintentionally) in the setting of a stable body burden; with tissue saturation, any additional amount of lithium leads to signs and symptoms of toxicity.

Acute Toxicity

Patients with acute lithium toxicity present predominantly with early GI symptoms. Neurologic manifestations are a late finding in acute toxicity, as the lithium redistributes slowly into the CNS.

Lithium is associated with a number of electrocardiographic abnormalities that are generally of little clinical consequence. The most commonly reported manifestation is T-wave flattening or inversion, primarily in the precordial leads. Prolongation of the QTc, sinoatrial nodal dysfunction, and bradycardia may occur. Malignant dysrhythmias or significant dysfunction is very rare.

Chronic Toxicity

Patients with chronic overexposure to lithium present with predominantly neurologic findings. It is important to note that neurotoxicity does not correlate with serum concentrations. The initial clinical condition of the patient and the duration of exposure to an elevated concentration seem to be closely predictive of outcome more than the initial serum lithium concentration.

Mental status is often altered and can progress from confusion to stupor, coma, and seizures. Tremor, fasciculations, hyperreflexia, choreoathetoid movements, clonus, dysarthria, nystagmus, and ataxia may occur. The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is a descriptive syndrome of the irreversible neurologic and neuropsychiatric sequelae of lithium toxicity. SILENT is defined as neurologic dysfunction caused by lithium in the absence of prior neurologic illness, which persists for a period of at least 2 months following cessation of the drug. Because of the polypharmacy prevalent in psychiatric treatment, long-term neurologic sequelae attributed to lithium are generally described in patients using lithium in combination with other medications such as antipsychotics, carbamazepine, phenytoin, valproic acid, and others. There seems to be a predominance of cerebellar findings in SILENT. One of the predictors of persistent neurologic dysfunction seems to be the concomitant finding of hyperthermia, an ominous finding in lithium toxicity.

Acute-on-Chronic Toxicity

Patients on chronic therapy who acutely ingest an additional amount of lithium, either intentionally or unintentionally, are at risk for signs and symptoms of both acute and chronic toxicity.

Other Adverse Effects

The most common adverse effect of chronic lithium therapy is the development of nephrogenic diabetes insipidus. The process thought to be involved is the interference of lithium vasopressin-sensitive mechanisms in the kidney, leading

to reduced expression of the vasopressin-regulated water channel aquaporin-2 (AQP2), making the distal tubules resistant to the action of vasopressin.

Chronic lithium therapy is also associated with a chronic tubulointerstitial nephropathy, as manifested by the development of renal insufficiency with little or no proteinuria, and biopsy findings of tubular cysts.

Lithium is also associated with a number of endocrine disorders, particularly hypothyroidism and hyperparathyroidism. Lithium causes a leukocytosis and an increase in neutrophils.

In utero exposure to lithium increases the incidence of congenital heart defects, specifically Ebstein anomaly.

DIAGNOSTIC TESTING

Because of the prevalence of lithium use, therapeutic drug monitoring is readily available in most settings. A lithium concentration should be requested upon patient presentation and serial measurements requested in patients with sustained-release ingestions. Note that serum lithium concentrations may not be representative of the concentration of lithium in the brain. Emphasis should be placed upon the lithium concentration as a marker of exposure, not necessarily as a determinant of therapy. Caution should be made that the concentration is sent in an appropriate, lithium-free tube, as certain lithiated-heparin tubes can exaggerate the concentration or give false-positive results. Serum electrolytes including renal function should be monitored as renal function is important in determining the need for and safety of aggressive therapy, including enhanced elimination technique such as hemodialysis. An electrocardiogram should generally be performed.

MANAGEMENT

Lithium rarely if ever affects the airway or breathing of the patient, although coingestants may. The formulation and nature of the product should be ascertained as immediate- or sustained-release. Information should be obtained concerning whether or not lithium is part of the patient's medication regimen, so as to determine whether the exposure is acute, acute-on-chronic, or chronic.

Gastrointestinal Decontamination

With an acute overdose of an immediate-release preparation, self-decontamination through emesis may have already occurred. Lithium, in immediate-release preparations, is rapidly absorbed, limiting the benefit of additional gastrointestinal evacuation.

Sustained-release preparations are generally too large to be removed by an orogastric lavage hose, and this modality has no role in the acute management of a lithium overdose, unless indicated for a coingestant.

Lithium does not bind readily to activated charcoal. Unless indicated for another ingested xenobiotic, there is little role for activated charcoal.

Sodium polystyrene sulfonate (SPS) is a cationic exchange resin often used for the treatment of severe hyperkalemia. Although typically used for enhancing the elimination of serum potassium in hyperkalemic patients, lithium may bind to the resin and lower serum concentrations. However, the dose of SPS needed for clinically beneficial lithium removal is unrealistic and associated with marked hypokalemia. At present, the use of SPS in the management of the lithium-poisoned patient cannot be recommended.

Whole-bowel irrigation (WBI) is the only GI decontamination modality that has shown substantial efficacy in eliminating lithium from human subjects, but its use is limited to those patients who ingest sustained-release preparations.

Fluid and Electrolytes

The critical initial management of the lithium-poisoned patient should focus on restoration of intravascular volume both in patients with acute poisonings, who have gastrointestinal losses, and in those with chronic poisoning, who have disturbed renal function. This can be managed by the initiation of an infusion of 0.9% sodium chloride solution at a rate of 1.5–2 times the maintenance rate. This increases perfusion of the kidney, increasing the GFR, and the elimination of lithium. The urine output and electrolytes must be closely monitored.

Lithium-induced nephrogenic diabetes insipidus can be corrected by discontinuation of the drug and through repletion of electrolytes and free water.

Attempts to enhance elimination of lithium through forced diuresis with loop diuretics (furosemide), osmotic agents (mannitol), carbonic anhydrase inhibitors (acetazolamide), or phosphodiesterase inhibitors (aminophylline) should be avoided. Although an initial, small increase in elimination may be achieved, all typically result in dehydration and increase retention of lithium.

Extracorporeal Drug Removal

Debate surrounds the efficacy and practicality of using enhanced elimination techniques in cases of lithium poisoning. Lithium is efficiently cleared by hemodialysis. However, when intermittent hemodialysis is used for patients with chronic lithium toxicity, clearance of the plasma compartment is often followed by a rebound phenomenon of redistribution from tissue stores leading to increased plasma concentrations. Conceptually, this may represent the movement of lithium out of the CNS.

Hemodialysis is indicated for lithium-poisoned patients manifesting severe signs and symptoms of neurotoxicity, such as alterations in mental status, and for those with renal failure or other factors that complicate aggressive intravascular volume loading.

Although serum concentrations do not necessarily correlate with toxicity, those patients with a lithium concentration greater than 4.0 mEq/L with any type of overdose, or a level of greater than 2.5 mEq/L with a chronic overdose, should have hemodialysis.

The dialysate bath should contain bicarbonate as opposed to acetate as this will help lessen the intracellular sequestration of lithium that occurs as a consequence of the activation of the sodium-potassium antiporter, with preferential intracellular transport of lithium.

Continuous venovenous hemodialysis and hemodiafiltration (CVVHD and CVVHDF) are 2 continuous renal replacement therapies (CRRT) that may be used in the treatment of lithium poisoning. Peritoneal dialysis is ineffective.

69 Monoamine Oxidase Inhibitors

HISTORY AND EPIDEMIOLOGY

The monoamine oxidase inhibitors (MAOIs) were first used in the early 1950s to treat tuberculosis and hypertension. When their mood-elevating properties were recognized, they were subsequently prescribed for the treatment of depression. Despite their effectiveness, the use of MAOIs was limited by potential food and drug interactions. In the 1970s, the MAOIs were largely replaced by tricyclic antidepressants but still remain in use for the treatment of refractory depression, phobias, and anxiety disorders. The new MAOIs are notably safer in overdose and have limited food and drug reactions. Natural MAOIs can be found in plants such as St. John's wort and Syrian rue (containing harmaline).

PHARMACOLOGY

The biogenic amines tyramine, epinephrine, norepinephrine, dopamine, and serotonin are monoamines, that is, molecules containing a single amine group. Monoamine oxidase (MAO) is a flavin-containing enzyme that deactivates biologically active monoamines. MAO is found in a wide variety of organs, particularly in the nerve terminals of the CNS, the mitochondrial membrane of hepatocytes, the GI tract, and platelets.

MAO degradation of monoamines helps regulate presynaptic neurotransmitter stores. Thus, MAO inhibition elevates synaptic neurotransmitter concentrations. MAO in the gut degrades ingested biologically active amines before they can enter the systemic circulation.

MAOIs can be classified as *selective* versus *nonselective* and *reversible* versus *irreversible*. Selectivity refers to an MAOI's ability to differentiate between the 2 MAO enzyme subtypes, MAO-A and MAO-B. MAO-A is found in the liver, in the GI tract, and in monoaminergic neurons. Hepatic MAO-A is important in inactivating ingested monoamines such as tyramine. MAO-B is found primarily in the brain and in platelets. The nonselective MAOIs include phenelzine, isocarboxazid, and tranylcypromine. Selective MAOIs include pargyline, clorgyline, selegiline, and moclobemide.

Irreversible MAOIs, such as phenelzine, isocarboxazid, tranylcypromine, selegiline, and clorgyline, bind covalently to MAO, inhibiting the enzyme's function until new MAO is synthesized, a process that takes days to occur. Reversible MAOIs inhibit competitively such that complete MAO function can resume just hours after ingestion. Moclobemide and most newer MAOIs are reversible.

Other enzyme systems inhibited by MAOIs include diamine oxidase, pyridoxal phosphokinase, ceruloplasmin, dopa decarboxylase, L-glutamic acid decarboxylase, and other pyridoxine (B_6)-containing enzyme systems.

PHARMACOKINETICS AND TOXICOKINETICS

MAOIs are currently only available in oral form. They are well absorbed and peak concentrations are reached within 2–3 hours. MAOIs are hepatically

metabolized, primarily by acetylation, and are excreted in the urine. Some MAOIs are structurally related to amphetamine and have amphetaminelike activity unrelated to the inhibition of MAO. In addition, selegiline is metabolized to amphetamine and methamphetamine.

MONOAMINE OXIDASE INHIBITOR OVERDOSE

Significant morbidity and a high risk of mortality are expected in patients who overdose on one of the older, irreversible MAOIs. Mortality has been reported from acute ingestions of as little as 170 mg of tranylcypromine and 375 mg of phenelzine. Although fatalities have been reported with overdose with the reversible inhibitors of MAO-A (RIMAs), most overdoses are relatively benign because of their greater therapeutic window. Ingestion of <2000 mg of moclobemide, one of the new reversible MAOIs, typically results in mild or no symptoms.

Clinical Manifestations

The onset of symptoms may be delayed following acute overdose. As such, asymptomatic patients with presumed MAOI overdose require a minimum of 24 hours of monitoring for the delayed development of toxicity.

Patients present with irritability, anxiety, flushing, diaphoresis, tachycardia, and headache. More severe overdose produces hyperthermia, hypertonia, seizures, and marked hypertension. Other symptoms may include tachypnea, nystagmus, opsoclonus, mydriasis, hallucinations, trismus, neuromuscular irritability, agitation, and delirium. These effects are attributed to elevation of monoaminergic neurotransmitter concentrations and amphetaminelike activity. Severe overdoses progress to cardiovascular collapse with hypotension, dysrhythmias, marked hyperthermia, obtundation, disseminated intravascular coagulopathy, and multiorgan failure. These late findings are presumed secondary to catecholamine depletion and complications of hyperthermia. Secondary problems from CNS and hemodynamic hyperactivity can include dehydration, rhabdomyolysis, renal failure, myocardial infarction, intracranial hemorrhage, and ischemia.

Treatment

Therapy of patients with MAOI overdose should focus on emergency treatment of the airway followed by stabilization of the heart rate, blood pressure, and, subsequently, hyperthermia, seizures, and muscular rigidity. Most patients should receive activated charcoal, although orogastric lavage followed by activated charcoal would be indicated early following a significant ingestion.

Because hypertension often rapidly progresses to hypotension, preference should be given to titratable drugs with a rapid onset and termination of action such as sodium nitroprusside and nitroglycerine. The short-acting α-adrenergic antagonist phentolamine can also be given as a 2–5 mg IV bolus over several minutes. β-Adrenergic antagonists are contraindicated because of the potential for unopposed α-adrenergic vasoconstriction. When hypotension develops, dopamine should be avoided because its effects are dependent on release of presynaptic catecholamines. As a result, it can be either ineffective or produce paradoxically severe hypertension. Direct-acting catecholamines, such as norepinephrine, are preferred.

Hyperthermia should be aggressively treated with ice bath, and benzodiazepines should be used as adjuncts to control muscular rigidity, seizures, and

agitation that may be contributing to the hyperthermia and tachycardia. Barbiturates and neuromuscular blockers may also be required for patients with ongoing seizures. Vitamin B_6 should be given to replete potentially depleted stores in patients with refractory seizures, particularly if a hydrazine-derived MAOI such as phenelzine has been ingested. Although dantrolene has been used in MAOI overdose, it should not be considered the standard of care.

Secondary problems should be treated as they arise. These include treatment of rhabdomyolysis, renal failure, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), myocardial infarction, and intracranial hemorrhage.

SEROTONIN SYNDROME

Chapter 70 discusses the serotonin syndrome in detail.

TYRAMINE-RELATED MAOI–FOOD INTERACTIONS

Food interactions occur when pharmacologically active dietary monoamines such as tyramine, phenylethylamines, and histamine are ingested by patients taking MAOIs.

Protein-rich foods are particularly likely to contain decarboxylating bacteria that convert amino acids into pharmacologically active monoamines. Tyramine acts in a manner similar to the indirect-acting sympathetic agents releasing stored norepinephrine, resulting in a hypertensive crisis. Ingestion of as little as 6 mg of tyramine may result in a significant vasopressor effect in the MAO-inhibited patient. This is 1–10% of the amount normally needed to achieve a vasopressor effect. Much less danger of a tyramine reaction occurs with the use of the RIMAs and MAO-B selective agents. Table 69–1 lists foods high in tyramine content.

TABLE 69–1. Dietary Restrictions for Patients Taking MAOIs

High tyramine content
Aged, mature cheeses (65–1500 mg/kg)
Smoked, pickled, aged, putrefying meats or fish (0–470 mg/kg)
Yeast and meat extracts (65–2250 mg/kg)
Red wines (1.5–12 mg/kg)
Broad beans
Moderate tyramine content
Meat extracts (100–300 mg/kg)
Pasteurized light and pale beers
Avocados
Low tyramine content
Distilled alcohol
Cottage cheese, cream cheese
Sour cream
Chocolate, caffeine-containing beverages
Fruit
Soy sauce
Yogurt

Patients should avoid high tyramine–content meals, eat small quantities of meals containing moderate amounts of tyramine, and may eat foods low in tyramine content.

Clinical Manifestations

Symptoms of MAOI–food interactions develop rapidly after ingestion and include hypertension, tachycardia, headache, and flushing. Severe reactions progress to altered mental status and seizures and complications from uncontrolled hypertension, such as myocardial infarction and intracranial hemorrhage. Fortunately, ingested monoamines have a short half-life and the direct effects abate within several hours.

Treatment

Symptomatic hypertension (including headache) should be treated with short-acting agents such as phentolamine or nitroprusside. Many clinicians also use calcium channel blockers. Unlike essential hypertension, these patients develop severe symptoms with relatively modest increases in blood pressure. Likewise, there should be little concern over complications that might result from restoring normal blood pressure, as these patients should all be presumed to have been normotensive immediately prior to their reactions. Patients who develop an altered mental status, seizures, or persistent headache should have neuroimaging to exclude intracranial hemorrhage.

ADVERSE DRUG EVENTS

Adverse drug events associated with MAOIs are so significant and complex that no medication should be introduced in a patient already on an MAOI without specifically checking for potential interactions. Drug interactions with indirect-acting sympathomimetic agents present in a similar fashion to MAOI–food interactions, with hypertension and headache being the most common findings. Treatment is as described above.

The MAOIs also inhibit the mixed-function oxidase enzyme system of cytochrome P450 that metabolizes and inactivates pentobarbital, amobarbital, and hexobarbital. Consequently, doses of barbiturates should be decreased when MAOIs are used simultaneously. Similarly, the sedating effects of codeine may be prolonged and potentiated in MAO-inhibited patients. Medications in other classes that might necessitate dose reduction because of prolonged and intensified effects in the setting of MAO inhibition include general anesthetics, sedatives, antihistamines, ethanol, and anticholinergics.

70 Serotonin Reuptake Inhibitors and Atypical Antidepressants

HISTORY AND EPIDEMIOLOGY

Most antidepressants inhibit the reuptake of serotonin and/or norepinephrine as a means to achieve their therapeutic effect. The class of serotonin reuptake inhibitors (SRIs) includes citalopram, escitalopram (active enantiomer of citalopram), fluoxetine, fluvoxamine, paroxetine, and sertraline.

Initially marketed in the United States in the early 1980s, SRIs are still considered a first-line therapy for the treatment of depressive disorders. SRIs are as effective as the tricyclic antidepressants for the treatment of major depression, and have less significant side effects. As such, they have become the largest prescribed class of medication for depression. The relative safety of the SRIs in an overdose, when compared with cyclic antidepressants and monoamine oxidase inhibitors, also makes them desirable.

PHARMACOLOGY, PHARMACOKINETICS, AND TOXICOKINETICS

Table 70–1 lists the pharmacology, therapeutic doses, and metabolism of the currently available SRIs and other atypical antidepressants. Unlike tricyclic antidepressants and other atypical antidepressants, SRIs have little direct interaction with cholinergic receptors, γ-aminobutyric acid (GABA) receptors, sodium channels, or adrenergic reuptake (Table 70–2).

Important pharmacokinetic and pharmacodynamic drug interactions are reported with therapeutic dosing. (Pharmacodynamic interactions are listed under Serotonin Syndrome below.) The SRIs and their active metabolites are substrates for, and potent inhibitors of, the CYP2D6 and other cytochrome P450 (CYP) isozymes. The consequences of these interactions are manifest when the metabolism of xenobiotics that rely on these isozymes for metabolic transformation is altered (Chap. 9).

CLINICAL MANIFESTATIONS

Acute Overdose

The majority of the effects that occur following overdose are a direct extension of the pharmacologic activity of SRIs in therapeutic doses. Acute signs and symptoms include nausea, vomiting, dizziness, blurred vision, and, less commonly, CNS depression and sinus tachycardia. Seizures and QRS complex prolongation are also reported, but are rare with most SRIs, even after large overdoses (Table 70–3).

Citalopram

Citalopram and its enantiomer escitalopram increase the QTc interval and cause seizures in a dose-related manner. These effects are reported in doses as low as 400 mg of citalopram. In one case series, seizures were an early finding, whereas the development of ECG abnormalities was delayed for as long as 24 hours following ingestion. The didesmethylcitalopram metabolite of citalopram prolongs the QTc by blocking I_{Kr}, whereas high levels of both the parent drug and this metabolite result in seizures.

TABLE 70–1. Drug Mechanism and Drug Information for Currently Available SRIs and Atypical Antidepressants

Drug	Typical Daily Dose Range (mg)	Vd (L/kg)	$t_{1/2}$ (h)	Major Metabolic Isozyme	Major Active Metabolites	Major Active Metabolite $t_{1/2}$	Drug (d) or Metabolite (m) Inhibits CYP
Selective serotonin reuptake inhibitors (SSRI)							
Citalopram	20–60	12–15	33–37	2C19, 3A4, 2D6	Monodesmethylcitalopram, didesmethylcitalopram	59 h	None/unknown
Escitalopram	10–20	19	22–32	2C19, 3A4, 2D6, 2C9, 2D6	S(+)-Desmethylcitalopram	59 h	None
Fluoxetine	10–80	14–100	24–144		Norfluoxetine	4–16 d	2D6 (d, m), 2C19 (d, m), 2D6 (d, m), 3A4 (m)
Fluvoxamine	100–300	25	15–23	1A2, 2D6	None	N/A	1A2, 2C9, 2C19, 3A4
Paroxetine	10–50	8–28	2.9–44	2D6	None	N/A	2D6
Sertraline	50–200	20	24	2C9, 2B6, 2C19, 2D6, 3A4	Desmethylsertraline	62–104 h	2C19 (d, m)
SRI with α_1-adrenergic antagonism							
Trazodone	50–600	0.47–1	3–9	2D6, 3A4 inhibitors may increase concentration	Metachlorophenylpiperazine	?	None/unknown
Nefazodone	200–600	0.22–0.87	2–4	3A4	Hydroxynefazodone	?	3A4

SRI with inhibition of reuptake of norepinephrine							
Venlafaxine	75–375	6–7	3–4	2D6	*O*-desmethylvenlafaxine, depends on 3A4 and 2C19 for metabolism	10 h	None/unknown
Duloxetine	40–60	23	8–17	2D6,1A2	4-hydroxyduloxetine, 5-hydroxy, 6-methoxyduloxetine sulfate (unknown if active)	?	2D6
SRI with α_2-adrenergic antagonism: 5-HT$_2$/5-HT$_3$ antagonism							
Mirtazapine	15–45	?	20–40	3A4	Desmethylmirtazapine	?	
Inhibition of reuptake of biogenic amines or dopamine							
Bupropion	150–450	20	9.6–20.9	2D6	Hydroxybupropion, erythrohydrobupropion, threohydrobupropion	24–37 h	None/unknown

TABLE 70–2. Receptor Activity of SSRIs and Related Antidepressants

Drug	Mechanism	Degree of Norepinephrine Reuptake Inhibition	Degree of Effect on Serotonin	Degree of Dopamine Reuptake Inhibition	Degree of Peripheral α-Adrenergic Agonism
SSRIs					
Citalopram	SSRI, antimuscarinic	0	+ + + +	0	0
Escitalopram	SSRI	0	+ + + +	0	0
Fluoxetine	SSRI	0	+ + + +	0	0
Fluvoxamine	SSRI	0	+ + + +	0	0
Paroxetine	SSRI, antimuscarinic	+	+ + + +	+	0
Sertraline	SSRI	0	+ + + +	+	+
Other					
Bupropion	Inhibits reuptake of biogenic amines	+ +	+	+	+ + +
Duloxetine	SRI, norepinephrine reuptake inhibitor	+ +	+ + + +	0	+ +
Mirtazapine	α_2-Adrenergic antagonism, 5-HT_2/5-HT_3 antagonism	0	+ + + +	0	+
Reboxetine	Selective norepinephrine reuptake inhibitor	+ + + +	0	0	+ + + +
Nefazodone	SRI, α-adrenergic antagonist	+ +	+	+	0–+
Tianeptine	Unclear	?	?	?	?
Trazodone	SRI, α-adrenergic antagonist	0	+ + + +	0	0–+
Venlafaxine	SRI, norepinephrine reuptake inhibitor	+ +	+ + + +	0	+ +

SSRI = selective serotonin reuptake inhibitor; SRI = serotonin reuptake inhibitor.
+ weak if any agonism; + +, weak agonism; + + +, strong agonism; + + + +, very strong agonism; 0, no effect.

TABLE 70–3. Predictive Analysis of the Relative Potential for Seizures and ECG Abnormalities of SRIs and Related Antidepressants

Drug	Seizures	QTc Prolongation	QRS Prolongation
SRIs			
Citalopram	+ + +	+ + +	0–+
Escitalopram	+ + +	+ + +	0–+
Fluoxetine	+	0	0–+
Fluvoxamine	+	0	0–+
Paroxetine	+	0	0–+
Sertraline	+	0	0–+
Atypical antidepressants			
Bupropion	+ + + +	0–+	0–+
Duloxetine	+ + + +	Unknown	Unknown
Mirtazapine	Unknown	Unknown	+ +
Reboxetine	+ + + +	Unknown	Unknown
Tianeptine	Unknown	Unknown	Unknown
Trazodone	0–+	0	0
Venlafaxine	+ + +	0–+	+ + +

0 does not cause; + very rarely causes; + + rarely causes; + + + causes; + + + + very commonly causes.

Management

Treatment of patients with acute SRI overdose is largely supportive. Dextrose and thiamine should be considered in patients presenting with an alteration in mental status when clinically warranted. Although cardiac manifestations after SSRI overdose are rare, a 12-lead ECG should be obtained to identify other cardiotoxic drugs, such as tricyclic antidepressants (TCAs), to which the patient may have access. Patients who overdose on citalopram or escitalopram should have 24 hours of cardiac monitoring to exclude the possibility of QTc prolongation and subsequent risk for ventricular dysrhythmias. After the patient is stabilized, oral activated charcoal (1 g/kg) in a slurry may be useful for adsorbing drug remaining in the gastrointestinal tract. Because SRI overdose is rarely life-threatening, orogastric lavage is not generally indicated.

Adverse Effects after Therapeutic Doses

Adverse effects commonly attributed to therapeutic doses of SRIs that may also be present in overdose include GI symptoms (anorexia, nausea, vomiting, diarrhea), sexual dysfunction in both males and females, headache, insomnia, jitteriness, dizziness, and fatigue. The syndrome of inappropriate antidiuretic hormone (SIADH), in which severe hyponatremia may occur rapidly, is associated with SRI use. Women older than age 70 years who are concomitantly receiving diuretic therapy are at greatest risk of developing SIADH. Although reported to occur from 3 days to 4 months after the initiation of therapy, SIADH occurs most frequently within the first 2 weeks of therapy.

SEROTONIN SYNDROME

The most common severe adverse effect associated with SRIs is the development of serotonin syndrome. This syndrome was first described in patients treated with

monoamine oxidase inhibitors (MAOIs) who were given other drugs that enhance serotonergic activity. However, ingestion of an MAOI is not required for this syndrome to develop, and its development is unpredictable (Table 70–4).

Pathophysiology

The pathophysiologic mechanism of the serotonin (5-HT) syndrome is incompletely understood, but involves excessive selective stimulation of 5-HT_{2A}, and perhaps 5-HT_{1A}, receptors.

Clinical Manifestations

Symptoms of serotonin syndrome include altered mental status, agitation, myoclonus, hyperreflexia, diaphoresis, tremor, diarrhea, incoordination, muscle rigidity, and fever. Life-threatening effects invariably result from hyperthermia caused by excessive muscle activity. Sustained severe hyperthermia can result in lactic acidosis, rhabdomyolysis, myoglobinuria, renal and hepatic dysfunction, disseminated intravascular coagulation, adult respiratory distress syndrome, and death.

There is no currently available diagnostic test capable of determining whether a patient is experiencing serotonin syndrome. Table 70–5 highlights clinical criteria used to establish the diagnosis.

Management

Treatment for patients with serotonin syndrome begins with supportive care and focuses on decreasing muscle rigidity. Because this muscular rigidity is thought to be partly responsible for hyperthermia and death, rapid external

TABLE 70–4. Potential Causes of Serotonin Syndrome

Drugs that inhibit serotonin breakdown
Monoamine oxidase inhibitors (nonselective)
Phenelzine, moclobemide, clorgyline, isocarboxazid
Harmine and harmaline from Ayahuasca preparations, a psychoactive beverage used for religious purposes in the Amazon and Orinoco River basins
Drugs that block serotonin reuptake
Clomipramine
Cocaine
Dextromethorphan
Meperidine
Pentazocine
SSRIs
Fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline
Trazodone
Venlafaxine
Serotonin precursors or agonists
L–Tryptophan
Lysergic acid diethylamide (LSD)
Drugs that enhance serotonin release
Amphetamines, especially MDMA (ecstasy)
Buspirone
Cocaine
Lithium
Mirtazapine (?)

TABLE 70–5. Diagnostic Criteria for Serotonin Syndrome

Major	Minor
Mental status	
Consciousness altered	Restlessness
Elevated mood	Insomnia
Coma	
Other neurologic signs and symptoms	
Coma	Incoordination
Myoclonus	Mydriasis
Tremor	Akathisia
Shivering	
Rigidity	
Hyperreflexia	
Vital signs and autonomic manifestations	
Fever (Hyperthermia)	Tachycardia
Sweating	Tachypnea or dyspnea
	Diarrhea
	Hypertension or hypotension

- Serotonin syndrome is diagnosed by the presence of at least 4 major symptoms or 3 major plus 2 minor symptoms following the addition or an increase in a known serotonergic agent.
- An underlying psychiatric disorder should be excluded.
- Other etiologies must be excluded, including initiation of a neuroleptic or other dopamine antagonist or withdrawal from a dopamine agonist.

cooling in conjunction with the aggressive use of benzodiazepines should limit complications and mortality. In severe cases, neuromuscular blockade should be considered to achieve rapid muscle relaxation. The serotonin syndrome resolves in most patients within 24 hours after removal of the offending drug, but can be prolonged when caused by drugs with long half-lives, protracted duration of effects, or active metabolites.

Several case reports support the use of 4 mg of oral cyproheptadine, an antihistamine with nonspecific antagonist effects at 5-HT_{1A} and 5-HT_{2A} receptors. Further research is warranted to determine whether higher doses might be successful in more severely affected patients in order to gain sufficient 5-HT_{2A} antagonistic effects.

DIFFERENTIAL DIAGNOSIS OF THE SEROTONIN SYNDROME FROM THE NEUROLEPTIC MALIGNANT SYNDROME

There are many overlapping features between the serotonin syndrome and the neuroleptic malignant syndrome (NMS) (Chap. 67). Table 70–6 highlights these distinguishing characteristics.

ATYPICAL ANTIDEPRESSANTS

Atypical antidepressants are defined as not belonging strictly to a set classification of antidepressants. As such, they are not selective serotonin reuptake inhibitors, cyclic antidepressants, or monoamine oxidase inhibitors.

Serotonin/Norepinephrine Reuptake Inhibitors

In addition to inhibiting the reuptake of serotonin, venlafaxine inhibits the reuptake of norepinephrine. Patients acutely overdosed with venlafaxine may

TABLE 70–6. Comparison of Neuroleptic Malignant Syndrome (NMS) and Serotonin Syndrome (SS)

	NMS	SS
Historical diagnostic clue		
Inciting drug pharmacology	Dopamine antagonist	Serotonin agonist
Time course of initiation of symptoms after exposure	Days to weeks	Hours
Duration of symptoms	Days to 2 weeks	Usually 24 hours
Symptoms		
Autonomic instability	+ + +	+ + +
Fever	+ + +	+ + +
Altered mental status (depressed/confusion)	+ + +	+ + +
Altered mental status (agitation/hyperactivity)	+	+ + +
Lead pipe rigidity	+ + +	+
Tremor, hyperreflexia, myoclonus	+	+ + +
Shivering	–	+ + +
Bradykinesia	+ + +	–

– not found; + rare finding; + + + common finding.

present with nausea, vomiting, dizziness, tachycardia, CNS depression, hypotension, hyperthermia, hepatic enzyme elevations, and seizures. Sodium channel inhibition effects are rarely clinically apparent; however, QRS prolongation and ventricular tachycardia have resulted in death.

Duloxetine, a similar drug, has limited overdose information available thus far, but would be expected to result in similar effects.

Norepinephrine Reuptake Inhibitors

Reboxetine is a selective norepinephrine reuptake inhibitor. Lack of experience precludes an analysis of overdose data. However, toxicity can be extrapolated from adverse effects reported in clinical trials and from experience with other drugs possessing similar pharmacologic characteristics. In particular, overdosed patients should be carefully monitored for tachycardia, hypertension or hypotension, and the development of seizures.

Other Atypical Agents with Reuptake Inhibition as Part of Their Mechanism

The pharmacologic mechanism of action of bupropion, a unicyclic antidepressant, is unclear, but both the parent drug and an active metabolite inhibit the reuptake of dopamine and, to a lesser extent, serotonin and norepinephrine. Chronic doses greater than 450–500 mg/d place the patient at risk of seizures. Frequent effects after overdose include tachycardia, hypertension, GI symptoms, and agitation. Large, acute overdoses may result in seizures with or without QRS complex prolongation. In some cases, these effects were delayed for up 10 hours, particularly after ingestion of sustained-release preparations.

Treatment, when required for seizures, should be supportive and include the judicious use of benzodiazepines, followed by barbiturates. If QRS pro-

longation occurs, the patient should be treated with sodium bicarbonate. Early after sustained-release bupropion overdose, activated charcoal should be considered, with multiple doses of activated charcoal or whole-bowel irrigation used after large, potentially life-threatening ingestions.

Trazodone is a serotonin agonist that acts through inhibition of serotonin reuptake. In addition, trazodone may have some peripheral α-adrenergic antagonist activity. Central nervous system depression and orthostatic hypotension are the most common complications after acute overdose of trazodone. Management includes supportive care and fluids, and vasopressors, if necessary.

The mechanism of action of mirtazapine is unique in that in addition to serotonin reuptake inhibition, it increases neuronal norepinephrine and serotonin through α_2-adrenergic antagonism. Mirtazapine also blocks 5-HT_2 and 5-HT_3 receptors, which appear to have antidepressant effects. The main effects that occur after acute overdoses of mirtazapine include the alteration of mental status and tachycardia. Large overdoses may cause respiratory depression and prolongation of the QTc.

DRUG DISCONTINUATION SYNDROME

A drug discontinuation syndrome is defined as withdrawal manifestations that are pharmacologically based and occur after the therapeutic use of a drug. Drug discontinuation syndromes are commonly reported after acute withdrawal of conventional antidepressants, including tricyclic antidepressants and monoamine oxidase inhibitors. Selective serotonin reuptake inhibitors also cause a discontinuation syndrome that typically begins within 5 days after drug discontinuation and that may last up to 3 weeks. The most frequently reported symptoms include dizziness, lethargy, paresthesia, nausea, vivid dreams, irritability, and depressed mood. Discontinuation syndrome is more common with SSRIs with a shorter elimination half-life (paroxetine > fluvoxamine > sertraline > fluoxetine). In addition, those SSRIs with high-potency serotonin reuptake inhibition are more frequently implicated (paroxetine > sertraline > clomipramine > fluoxetine > venlafaxine > trazodone).

The biochemical basis of the discontinuation syndrome is hypothesized to result from serotonin receptor downregulation leading to alterations in serotonergic activity, including interactions with other neurotransmitters (GABA, norepinephrine, and dopamine). Treatment of patients exhibiting discontinuation symptoms should include supportive care and the reinitiation of the discontinued drug or another SSRI, if reinitiation of the drug is contraindicated. The drug should then be tapered at a rate that allows for improved patient tolerance.

71 Cyclic Antidepressants

HISTORY AND EPIDEMIOLOGY

Cyclic antidepressants (CAs) comprise a group of pharmacologically related drugs used in the treatment of depression, neuropathic pain, migraines, enuresis, and attention deficit hyperactivity disorder. From the 1960s until the late 1980s, the tricyclic antidepressants (TCAs) represented the major pharmacologic treatment for depression in the United States. However, by the early 1960s, the cardiovascular and central nervous system toxicity were also recognized as major complications of TCA overdoses. The newer cyclic antidepressants were developed in the 1980s and 1990s to decrease some of the adverse effects that occurred with older TCAs, improve the therapeutic index, and reduce the incidence of serious toxicity (Table 71–1).

The epidemiology of cyclic antidepressant poisoning has evolved significantly in the last 10 years, in great part as a result of the introduction of the newer selective serotonin reuptake inhibitors (SSRIs). Between 1993 and 1997, 95% of poisoning deaths in England and Wales were associated with TCAs, particularly dothiepin and amitriptyline. In the United States, TCAs were the leading cause of poisoning fatalities until 1993, when they were replaced by the analgesics as the primary cause of death.

PHARMACOLOGY

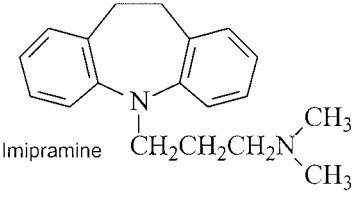
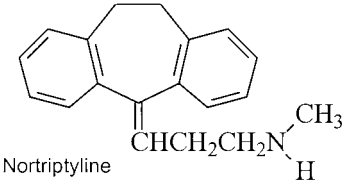
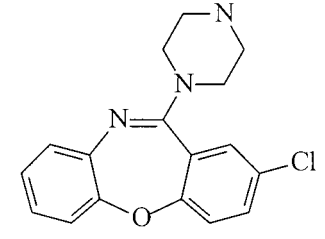
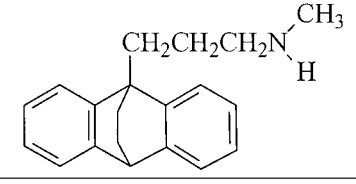
Therapeutically, cyclic antidepressants inhibit the presynaptic reuptake of norepinephrine and/or serotonin and thus functionally increase the amount of these neurotransmitters at central nervous system (CNS) receptors. Chronic TCA administration also alters the number and/or function of central β-adrenergic and serotonin receptors, modulates glucocorticoid receptor gene expression, and causes alterations at the genomic level of other receptors.

Additional pharmacologic mechanisms of CAs are responsible for their side effects and overdose presentations. All of the CAs are competitive antagonists of the muscarinic acetylcholine receptors, although with different affinities. The acetylcholine blockade is responsible for the central and peripheral anticholinergic adverse effects, such as dry mouth, urinary retention, blurred vision, and sedation. The CAs also antagonize peripheral α_1-adrenergic receptors, producing vasodilation and orthostatic hypotension. The membrane-stabilizing effect of CAs is responsible for cardiac conduction abnormalities that occur even in therapeutic doses and, following overdose, is the mechanism of life-threatening cardiac toxicity. Finally, CAs inhibit the γ-aminobutyric acid (GABA)-receptor chloride-ionophore complex.

PHARMACOKINETICS AND TOXICOKINETICS

Cyclic antidepressants are rapidly and almost completely absorbed from the gastrointestinal tract, with peak concentrations 2–8 hours after administration of a therapeutic dose. CAs are weak bases (high pK_a); thus, changes in acid–base status alter the proportion of ionized to nonionized drug. Cyclic antidepressants are highly lipophilic and possess large and variable volumes of distribution (15–40 L/kg). They are extensively bound to α_1-acid glycoprotein (AAG) in the serum.

TABLE 71–1. Cyclic Antidepressants—Classification by Chemical Structure

Tertiary Amines	
Amitriptyline Clomipramine Doxepin Imipramine Trimipramine	 Imipramine
Secondary Amines	
Desipramine Nortriptyline Protriptyline	 Nortriptyline
Amoxapine	
Maprotiline	

Elimination half-lives for therapeutic doses of CAs vary from 7–58 hours (54–92 hours for protriptyline), with even longer half-lives in the elderly. Finally, less than 5% of CAs are excreted by the kidney unchanged.

PATHOPHYSIOLOGY

The CAs block the rapid inward movement of sodium ions into the fast sodium channel, slowing phase 0 depolarization of the action potential in the distal His-Purkinje system, as well as the ventricular myocardium. Impaired

depolarization within the conduction system slows the propagation of ventricular depolarization, which is manifested as prolongation of the QRS interval on the electrocardiogram. This slowing of depolarization results in a rightward shift of the terminal QRS axis and the right bundle-branch block pattern that occurs on the ECG of patients who are exposed to CA. The associated hypotension is caused by direct myocardial depression, downregulation of adrenergic receptors, and peripheral vasodilation from α-adrenergic blockade.

The agitation, delirium, and depressed sensorium are primarily caused by the central anticholinergic effects of the drug. The pathophysiology of CA-induced seizures has not been fully delineated and may be a result of a combination of increased levels of monoamines (particularly norepinephrine), antidopaminergic properties, anticholinergic properties, inhibition of neuronal sodium channels, and inibition of GABA receptors.

CLINICAL MANIFESTATIONS OF TOXICITY

It is common for a patient to present to the emergency department with minimal clinical abnormalities and to then develop life-threatening cardiovascular and CNS toxicity within a couple of hours. The CAs have a low toxicity threshold; acute ingestions of 10–20 mg/kg of most CAs cause significant cardiovascular and central nervous system manifestations (therapeutic dose is 2–4 mg/kg/d). Thus, in adults, life-threatening overdose is usually associated with ingestions >1 g. However, in a 10-kg toddler, as few as two 50-mg imipramine tablets may cause significant toxicity.

Acute Cardiovascular Toxicity

Cardiovascular toxicity is primarily responsible for the morbidity and mortality attributed to CAs. Conduction delays include prolongation of the QRS complex duration and rightward shift of the terminal 40-msec QRS axis (T40-ms) (see Fig. 5–4). PR, QRS, and QTc prolongation can occur in the setting of therapeutic and toxic doses of TCAs. Sinus tachycardia is the most common dysrhythmia associated with CA toxicity and usually does not cause hemodynamic compromise. Ventricular tachycardia is the most common lethal ventricular dysrhythmia, although it may be difficult to distinguish this dysrhythmia from sinus tachycardia with aberrant conduction. Acutely poisoned patients with QRS widening usually have altered mental status. Hypoxia, acidosis, hyperthermia, seizures, and β-adrenergic agonists may predispose the patient to ventricular tachycardia. Refractory hypotension is probably the most common cause of death from CA overdose.

Acute Central Nervous System Toxicity

Seizures and altered mental status are the primary manifestations of central nervous system toxicity. Delirium, disorientation, agitation, and/or psychotic behavior with hallucinations may be present. These alterations in consciousness are then usually followed by lethargy, rapidly progressing to obtundation and coma. Cyclic antidepressant-induced seizures are usually generalized and brief, and most often occur within 1–2 hours of ingestion. Abrupt deterioration in hemodynamic status, namely, hypotension and ventricular dysrhythmias, may develop during or within minutes after a seizure. This results from seizure-induced acidosis exacerbating cardiovascular toxicity.

Anticholinergic and Other Clinical Toxicity

Anticholinergic effects can occur early or late in the course of TCA toxicity. Pupils may be dilated and poorly reactive to light. Other anticholinergic effects include dry mouth, dry flushed skin, hyperthermia, urinary retention, and ileus.

Unique Toxicity from "Atypical" Cyclic Antidepressants

Although the incidence of serious cardiovascular toxicity is lower in patients with amoxapine overdoses, the incidence of seizures is significantly greater than for the traditional TCAs. Moreover, seizures may be more frequent or status epilepticus may develop. Similarly, the incidence of seizures, cardiac dysrhythmias, and duration of coma is greater with maprotiline toxicity than with the TCAs.

DIAGNOSTIC TESTING

Diagnostic testing for CA poisoning primarily relies on indirect bedside tests (ECG) and on other nonspecific laboratory analyses. Quantification of CA concentration provides little help for the acute management of patients with CA overdose, but provides adjunctive information to support the diagnosis.

Electrocardiogram

Cyclic antidepressant toxicity results in distinctive and diagnostic electrocardiographic changes that may allow early diagnosis and targeted therapy when the clinical history and physical examination may be unreliable. The maximal limb lead QRS complex duration is an easily measured ECG parameter that is a sensitive indicator of toxicity. Of patients with a limb lead QRS interval of 100 msec or longer, 33% develop seizures. When the QRS duration prolongs to 160 msec, there is a 50% incidence of ventricular dysrhythmias (Fig. 71–1).

A terminal 40-ms axis between 120° and 270° is also associated with TCA toxicity and is a very sensitive and specific marker of drug effect. An abnormal rightward axis can be estimated by observing a negative deflection (terminal S wave) in lead I, and a positive deflection (terminal R wave) in lead aVR (see Fig. 5–4).

Laboratory

Quantitative determination of CA plasma concentration has limited usefulness in the immediate evaluation and management of patients with acute overdoses. However, CA concentrations exceeding 1000 ng/mL are usually observed in patients with significant clinical toxicity (coma, seizures, and dysrhythmias), although life-threatening toxicity has also been observed in patients with serum concentrations less than 1000 ng/mL.

MANAGEMENT

Because patients with CA poisoning can deteriorate very rapidly, early intubation is advised for patients with CNS depression and/or hemodynamic instability. The patient should be attached to a cardiac monitor, intravenous access should be secured, and a 12-lead ECG should be obtained on all patients.

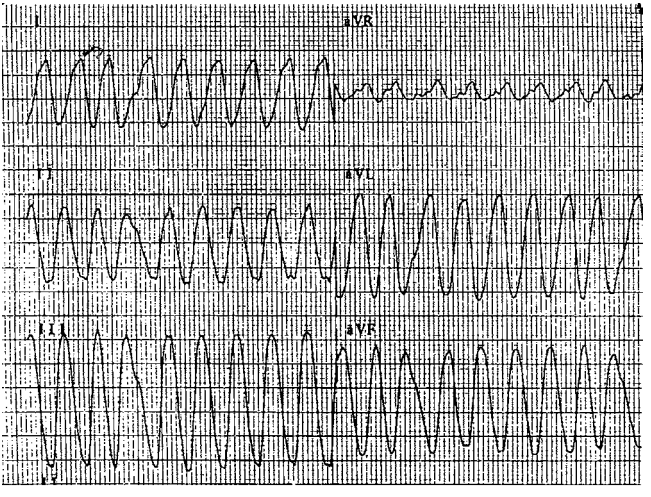


FIG. 71–1. Case electrocardiograms. Initial ECG shows a wide-complex tachycardia with a variable QRS duration (minimum 220 msec).

Gastrointestinal Decontamination

Induction of emesis is contraindicated. Orogastric lavage should be considered in symptomatic patients following intentional overdose. Because the anticholinergic actions of some CAs may decrease spontaneous gastric emptying, attempts at gastric lavage several hours after ingestion may yield unabsorbed drug. Patients with altered mental status or seizures should only undergo orogastric lavage after endotracheal intubation to protect the airway. Activated charcoal should be administered in nearly all cases.

Wide-Complex Dysrhythmias, Conduction Delays, and/or Hypotension

The mainstay therapy for treating wide-complex dysrhythmias, as well as for reversing conduction delays and hypotension, is the combination of serum alkalinization and sodium loading with hypertonic sodium bicarbonate. The optimal dosing and mode of administration of hypertonic sodium bicarbonate, is not well defined. A bolus, or rapid infusion over several minutes, of hypertonic sodium bicarbonate (1–2 mEq/kg) should be administered initially. Continuous ECG monitoring should be in place to follow the progression of the ECG abnormalities. Additional boluses every 3–5 minutes may be administered until the QRS interval narrows and the hypotension improves. Alternatively the patient can be placed on a continuous infusion. Blood pH should be monitored, aiming for a target pH of no greater than 7.50–7.55. Usually we recommend adding 3 ampules (132 mEq) of sodium bicarbonate to 1 L of 5% dextrose in water (D_5W) and infusing this fluid at twice maintenance.

Alkalinization may be continued for 12–24 hours after the ECG has normalized because of the drug's redistribution from the tissue. However, the time observed for resolution or normalization of conduction abnormalities is extremely variable, ranging from several hours to several days despite contin-

uous bicarbonate infusion. During this time frequent determinations of the serum potassium are required.

Antidysrhythmic Therapy

Following hypertonic sodium bicarbonate, lidocaine is the antidysrhythmic most commonly advocated for the treatment of CA-induced dysrhythmias, although there are no controlled human studies demonstrating its efficacy. The use of class IA (quinidine, procainamide, disopyramide, and moricizine) and class IC (flecainide, propafenone) antidysrhythmics are absolutely contraindicated because they have similar pharmacologic actions to CAs and thus may worsen the sodium channel inhibition and exacerbate cardiotoxicity. Phenytoin's use as an antidysrhythmic in CA toxicity has been extensively studied. Based on available evidence, phenytoin is not recommended for wide-complex tachydysrhythmias associated with CAs.

Hypotension

Standard initial treatment for hypotension should include volume expansion with isotonic saline, and alkalinization/sodium loading with hypertonic sodium bicarbonate (if conduction abnormalities also are present). Hypotension unresponsive to these therapeutic interventions necessitates the use of inotropic and/or vasopressor drug support, and possibly extracorporeal cardiovascular support. The α-adrenergic blockade and downregulation of receptors induced by CAs suggest that a direct-acting vasopressor such as norepinephrine is more efficacious than an indirect-acting catecholamine such as dopamine. If pharmacologic measures fail to correct hypotension, extracorporeal life support measures should be considered. Extracorporeal membrane oxygenation (ECMO), extracorporeal circulation (ECC), and cardiopulmonary bypass are successful adjuncts for refractory hypotension and life support when maximum therapeutic interventions fail.

Central Nervous System Toxicity

The use of flumazenil in the patient with a known or suspected CA ingestion is contraindicated. Physostigmine was used in the past to reverse the CNS toxicity of cyclic antidepressants. However, physostigmine is not recommended because it may increase the risk of cardiac toxicity and can cause bradycardia and asystole, as well as precipitate seizures in CA-poisoned patients. Seizures caused by cyclic antidepressants are usually brief and may stop before treatment can be initiated. Recurrent seizures, prolonged seizures (>2 minutes), and status epilepticus need prompt treatment to prevent worsening acidosis, hypoxia, and the development of hyperthermia and rhabdomyolysis. Benzodiazepines are effective as first-line therapy for seizures. If this therapy fails, barbiturates or propofol should be administered.

Enhanced Elimination

No specific treatment modalities have demonstrated clinically significant efficacy in enhancing the elimination of CAs. Some investigators propose multiple doses of activated charcoal to enhance CA elimination because of their small enterohepatic and enterogastric circulation, but experimental and clinical support for this practice are lacking. One additional dose of charcoal may be given in patients with evidence of significant CNS and cardiovascular toxicity if bowel sounds are present.

Hemodialysis is ineffective in enhancing the elimination of CAs because of their large volumes of distribution, high lipid solubility, and extensive protein binding. Hemoperfusion overcomes some of the limitations of hemodialysis, but is effective because of the large volumes of distribution of the CAs.

Hospital Admission Criteria

All patients who present with a known or suspected CA ingestion should receive continuous cardiac monitoring and serial electrocardiograms for a minimum of 6 hours. Fears of delayed complications and an inability to predict toxicity led clinicians in the past to adopt all-inclusive admission guidelines for the suspected CA ingestion. Most patients develop major clinical toxicity within several hours of presentation. If the patient is asymptomatic at presentation, undergoes gastrointestinal decontamination, has normal ECGs, or has sinus tachycardia (with normal QRS complex) that resolves, and remains asymptomatic in the healthcare facility for a minimum of 6 hours without any treatment interventions, the patient may be medically cleared for psychiatric evaluation or discharged home as appropriate.

Inpatient Cardiac Monitoring

Any patient with a prolonged QRS complex (>100 msec) requires intensive monitoring. The duration of cardiac monitoring is dependent on many factors. Based on the available literature, it is reasonable to recommend that after the mental status and blood pressure have normalized, patients should be monitored an additional 24 hours off all therapy, including alkalinization, antidysrhythmics, and inotropics/vasopressors. If the patient shows improvement of ECG abnormalities with the above criteria, the patient may be admitted to a monitored bed on the ward with a low risk of further complications.

72 Sedative-Hypnotics

Sedative-hypnotics are prescribed to induce a calming effect and limit excitability (sedative) or induce drowsiness and sleep (hypnotic). *Anxiolytics* or *tranquilizers* are other medical terms often used to describe sedative-hypnotics. The term *tranquilizer* has fallen out of favor because of a lack of precision, and the term *anxiolytic* is the preferred term because these medications diminish feelings of anxiety.

BACKGROUND

Intentional and unintentional overdoses with sedative-hypnotics are common. According to the American Association of Poison Control Centers, the sedative-hypnotic class is consistently one of the top five associated with, although not usually causative of, overdose fatalities (Chap. 130). With the ubiquitous worldwide use of sedative-hypnotics, they are probably also associated with substantially more deaths than are reported.

PHARMACOLOGY

All of the sedative-hypnotics produce CNS depression. Most clinically effective sedative-hypnotics produce their physiologic effects by enhancing the function of γ-aminobutyric acid (GABA)-mediated chloride channels. These alterations include increasing the frequency, as well as the duration, of opening of the GABA-mediated chloride channels. The varying effects of the sedative-hypnotics can be explained further by their action on the various GABA receptor subtypes. Sedative-hypnotics have variable affinities for certain GABA receptors with specific subunits (Chap. 14). $GABA_A$ receptors are the primary mediators of inhibitory neurotransmission in the brain.

Sedative-hypnotics not only increase the effects of GABA-mediated inhibitory neurotransmission, but also decrease the effects of glutamate-mediated excitatory neurotransmission, such as trichloroethanol. Barbiturates, benzodiazepines, etomidate, and propofol interact with *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)/kainate receptor function; barbiturates and propofol markedly attenuate the excitatory effects of glutamate. Benzodiazepines also inhibit adenosine metabolism and reuptake, thereby potentiating A_1-adenosine receptors and interact with serotonergic pathways.

PHARMACOKINETICS/TOXICOKINETICS

Clinical effects are determined by the relative ability of these drugs to penetrate the blood–brain barrier with the highly lipophilic ones penetrating fastest. The ultrashort-acting barbiturates are clinically active in the most vascular parts of the brain (gray matter first), with sleep occurring within 30 seconds of administration.

After initial distribution, many of the sedative-hypnotics undergo a redistribution phase as they are dispersed to other body tissues, specifically fat. The clinical activity of many of these drugs is determined by their rapid distribution and redistribution (alpha phase) and not by their elimination (beta phase) (Chap. 11).

Many of the sedative-hypnotics are metabolized to pharmacologically active intermediates. Benzodiazepines can be demethylated, hydroxylated, or conjugated with glucuronide in the liver. Glucuronidation proceeds rapidly with the production of inactive metabolites. Benzodiazepines, such as diazepam, undergo demethylation that yields active intermediates with a more prolonged therapeutic half-life than the parent compound. Because of the individual pharmacokinetics of sedative-hypnotics and the production of active metabolites, there is often no correlation between the therapeutic half-life and the biologic half-life (Table 72–1).

PHARMACODYNAMICS

Overdoses of combinations of sedative-hypnotics can be more toxic than an overdose of a single drug as synergistic clinical effects, mediated by diverse interactions on the GABA receptor may occur (Chap. 14). For example, both barbiturates and benzodiazepines act on the GABA site, but barbiturates prolong the opening of the chloride ionophore, whereas benzodiazepines increase the frequency of ionophore opening.

Tolerance

Ingestions of relatively large doses may not have the predicted effects in patients who chronically use sedative-hypnotics. These patients often develop tolerance defined as the progressive diminution of effect of a particular drug with repeated administrations. The majority of tolerance to sedative-hypnotics is caused by pharmacodynamic changes (Chap. 15). Cross-tolerance readily exists among the sedative-hypnotics.

Dependence and Withdrawal

Physical drug dependence refers to a condition where physiologic withdrawal is induced when a drug is suddenly stopped. All sedative-hypnotics produce dependence and withdrawal. Approximately one-third of chronic benzodiazepine users experience withdrawal when benzodiazepine use is suddenly decreased or discontinued. Factors that contribute to the severity of withdrawal include shorter half-life, higher daily dosage and the underlying medical and psychological illness (Chap. 15).

CLINICAL MANIFESTATIONS

Patients with significant sedative-hypnotic overdoses will manifest slurred speech, ataxia, and incoordination, a syndrome similar to ethanol intoxication. Those with moderate to severe toxicity are stuporous or comatose, and in the most severe cases, all neurologic responses may be lost. In general, respiratory depression parallels central nervous system depression. Hypoventilation produces respiratory acidosis and can contribute to cardiovascular depression.

Although the physical examination can rarely identify particular sedative-hypnotics, it can give clues to the class of sedative-hypnotics. Hypothermia has been described for most of the sedative-hypnotics, but may be more pronounced with barbiturates. Barbiturates may cause fixed drug eruptions that often are bullous in nature and appear over pressure point areas. However, this phenomenon is not specific to barbiturates and has been documented with other xenobiotics, including carbon monoxide, methadone, imipramine, glutethimide, and benzodiazepines. Methaqualone can cause muscular rigid-

TABLE 72–1. Pharmaceutical Sedative-Hypnotics

	Trade Name	Equipotent Dosing Oral Dose (mg)[b]	Plasma $t_{1/2}$	Protein Binding (%)	Vd (L/kg)	Active Metabolite Important
Benzodiazepines						
Agents with full agonist activity at the benzodiazepine site						
Alprazolam	Xanax	1.0	10–14	80	0.8	No
Chlordiazepoxide	Librium	50	5–15	96	0.3	Yes
Clorazepate	Tranxene	15	97	0.9	Yes	Unclear
Clonazepam	Klonopin	0.5	18–50	85.4	Unclear	Yes
Diazepam	Valium	10	20–70	98.7	1.1	Yes
Estazolam	ProSom	2.0	8–31	93	0.5	No
Flunitrazepam[a]	Rohypnol	1.0	16–35	80	1.0–1.4	Yes
Flurazepam	Dalmane	30	2.3	97.2	3.4	Yes
Lorazepam	Ativan	2.0	9–19	90	1–1.3	None
Midazolam	Versed	—	3–8	95	0.8–2	Yes
Oxazepam	Serax	30	5–15	Unclear	Unclear	No
Temazepam	Restoril	30	10–16	97	0.75–1.37	No
Triazolam	Halcion	0.25	1.5–5.5	90	0.7–1.5	Yes
Nonbenzodiazepine agents active mainly at the type I (ω_1) benzodiazepine site						
Eszopiclone	Lunesta	?	6	55	1.3	No
Zaleplon	Sonata	20	1.0	92	0.54	No
Zolpidem	Ambien	20	1.7	92	0.5	No
Barbiturates						
Amobarbital	Amytal	—	8–42	Unclear	Unclear	Unclear
Aprobarbital[a]	Alurate	—	14–34	Unclear	Unclear	Unclear
Butabarbital	Butisol	—	34–42	Unclear	Unclear	Unclear
Barbital[a]		—	6–12	25	Unclear	Unclear
Mephobarbital	Mebaral	—	5–6	40–60	Unclear	Yes

(continued)

TABLE 72–1. Pharmaceutical Sedative-Hypnotics *(continued)*

	Trade Name	Equipotent Dosing Oral Dose (mg)[b]	Plasma $t_{1/2}$	Protein Binding (%)	Vd (L/kg)	Active Metabolite Important
Methohexital	Brevital	—	3–6	73	2.2	Unclear
Pentobarbital	Nembutal	100	15–48	45–70	0.5–1.0	Unclear
Phenobarbital	Luminal	30	80–120	50	0.5–0.6	No
Primidone	Mysoline	—	3.3–22.4	19	Unclear	Yes
Secobarbital	Seconal	—	15–40	52–57	Unclear	Unclear
Thiopental	Pentothal	—	6–46	72–86	1.4–6.7	Unclear
Other						
Chloral hydrate	Aquachloral	NA	4.0–9.5	35–40	0.6–1.6	Yes
Ethchlorvynol[a]	Placidyl	NA	10–25	30–40	4	Unclear
Etomidate	Amidate	NA	2.9–5.3	98	2.5–4.5	Unclear
Glutethimide[a]	Doriden	NA	5–22	47–59	2.7	Unclear
Methprylon[a]	Nodular	NA	3–6	60	0.97	Unclear
Meprobamate[a]	Miltown	NA	6–17	20	0.75	Unclear
Methaqualone[a]	Quaalude	NA	19	80–90	5.8–6.0	Yes
Paraldehyde[a]	Paral	NA	7	Unclear	0.9	Unclear
Propofol	Diprivan	NA	4–23	98	2–10	No

NA = not applicable comparison.

[a]Not presently available in the United States.

[b]This table is an approximation of equipotent doses of drugs affecting the benzodiazepine receptor and several barbiturates. All of the full agonist benzodiazepines have similar amnestic, anxiolytic, sedative, and hypnotic effects. These effects are a reflection of dose and plasma concentration. There can be significant variation of these effects according to age and gender.

ity and clonus. Glutethimide can result in anticholinergic signs and symptoms. Patients with chloral hydrate overdoses present with both respiratory depression and cardiac toxicity, including, lethal ventricular dysrhythmias, caused by trichloroethanol, its active halogenated metabolite.

Early deaths as a consequence of barbiturate ingestions are caused by respiratory arrest and cardiovascular collapse, whereas delayed deaths are caused by acute renal failure, pneumonia, acute lung injury, cerebral edema, and multiorgan system failure.

Large doses of sedative-hypnotics given intravenously are associated with propylene glycol toxicity, including hypotension, hyperosmolar states, and metabolic acidosis. Fatal metabolic acidosis is associated with the carrier lipid of intravenous propofol.

DIAGNOSTIC TESTING

Laboratory testing, including electrolytes, liver enzymes, renal function, thyroid function tests, glucose, venous or arterial blood gas analysis, and cerebrospinal fluid (CSF) analysis, should be ordered as indicated. Diagnostic imaging studies, such as head CT scans, also may be warranted. Routine laboratory screening for "drugs of abuse" is generally not helpful. Many benzodiazepines are not detected by this assay, which typically identifies oxazepam or desmethyldiazepam.

Specific laboratory concentrations may be helpful, as in the case of alcohol or phenobarbital, to confirm or disprove overdoses. However, specific concentrations of sedative-hypnotics other than phenobarbital are not routinely performed. Abdominal radiographs might detect gastrointestinal chloral hydrate.

MANAGEMENT

Deaths secondary to sedative-hypnotic overdose are a result of cardiorespiratory collapse; consequently, careful attention should be focused on monitoring and maintaining adequate airway, oxygenation, and hemodynamic support. Hemodynamic instability should be approached with volume expansion, and vasopressors should be used only if there is no improvement. In the setting of cardiac dysrhythmias caused by chloral hydrate, judicious use of β-adrenergic antagonists is recommended.

Gastrointestinal Decontamination

All clinically stable patients with significant ingestions should receive activated charcoal. Multiple-dose activated charcoal increases the elimination of phenobarbital by 50–80%.

Orogastric lavage should be considered in patients whose overdose either may slow gastrointestinal motility or result in concretions, specifically in the cases of phenobarbital and meprobamate.

Antidotes

Flumazenil, a competitive benzodiazepine antagonist rapidly reverses the sedative effects of benzodiazepines. However, the use of flumazenil has a poor risk-to-benefit ratio in patients who present with a depressed mental status and who have an undifferentiated overdose (see Antidotes in Brief: Flumazenil).

Other than respiratory support, there are very few situations where a patient with sedative-hypnotic overdose requires invasive therapy. Hemodialy-

sis should be considered in patients with chloral hydrate overdose who develop life-threatening cardiac manifestations and patients with ingestions of extremely large quantities of phenobarbital and meprobamate who would otherwise require prolonged intubation times.

SPECIFIC MEDICATIONS

Barbiturates

Barbiturates are all derivatives of barbituric acid, which itself has no CNS depressant properties. Various side chains influence lipophilicity, potency, and rate of elimination. Elimination of phenobarbital, a long-acting barbiturate with a relatively low pK_a (7.24), can be influenced by the alkalinization of the urine with sodium bicarbonate to maintain a urinary pH of 7.5–8.0, which increases the amount of phenobarbital excreted by 5–10-fold.

Similar to other sedative-hypnotics, patients with significant barbiturate overdoses present with CNS and respiratory depression. Hypothermia and cutaneous bullae are often present. Although both these signs are described in other sedative-hypnotic overdoses, they may be more pronounced with barbiturates.

Benzodiazepines

Benzodiazepines are used principally as anxiolytics. Temazepam and triazolam are used as hypnotics. Clonazepam is used as a maintenance anticonvulsant. Benzodiazepines rarely cause paradoxical psychological effects such as nightmares, delirium, psychosis, and transient global amnesia. In addition to their effects at central nervous system $GABA_A$ receptors, benzodiazepines also are active at certain types of peripheral benzodiazepine receptors. Although presently termed *peripheral*, they are also located in the brain. Peripheral benzodiazepine receptors are found throughout the body with the greatest concentrations located in steroid-producing cells in the adrenal gland, anterior pituitary gland, and the reproductive organs. Although the exact role of these receptors remains unclear, it is postulated that benzodiazepines may influence basic cellular function, such as mitochondrial respiratory control, cell growth, and cell differentiation. Peripheral benzodiazepine receptors may be of significance in modulating pathologic conditions, such as hepatic encephalopathy, anxiety disorders, and abnormal immune function. Theoretically, cardiac benzodiazepine receptors support the use of benzodiazepines in the treatment chloroquine and cocaine cardiotoxicity.

Another unique property of the benzodiazepines is their relative safety even following substantial ingestion. Benzodiazepines are not known to cause any specific systemic injury, and their long-term use is not associated with specific organ toxicity. Deaths solely caused by benzodiazepine ingestions are extremely rare; most often deaths are secondary to a combination of alcohol or other sedative-hypnotics.

Abrupt discontinuation following long-term use of benzodiazepines may precipitate benzodiazepine withdrawal, which is characterized by autonomic instability, changes in perception, paresthesias, headaches, tremors, and seizures.

Chloral Hydrate

Chloral hydrate is metabolized by hepatic alcohol dehydrogenase. Trichloroethanol, the first active metabolite of chloral hydrate, is lipid soluble and is responsible for the hypnotic effects of chloral hydrate. Trichloroethanol has a

plasma half-life of 4–12 hours and is metabolized to inactive trichloroacetic acid by alcohol and aldehyde dehydrogenases.

Acute chloral hydrate poisoning is atypical of the other sedative-hypnotics. Cardiac dysrhythmias appear to be the main cause of death. Standard antidysrhythmics are often ineffective. A β-adrenergic antagonist is currently considered the drug of choice for the treatment of most dysrhythmias secondary to chloral hydrate toxicity. Chloral hydrate is radiopaque and can be occasionally detected on radiographs.

Methaqualone

The use of methaqualone as a mood "elevator" led to extensive abuse and its subsequent withdrawal from the market in the United States. Unlike many of the other sedative-hypnotics, hyperreflexia, clonus, and significant muscular hyperactivity can occur. Paresthesias and polyneuropathies can be a residual effect after overdoses.

Meprobamate/Carisoprodol

Carisoprodol is metabolized to meprobamate. Like barbiturates, meprobamate can directly open the GABA-mediated chloride channel and may inhibit NMDA receptor currents. Of all the nonbarbiturate tranquilizers, meprobamate is the most likely to produce euphoria. Large masses or bezoars of pills have been noted in the stomach at autopsy, and may lead to cyclical or recurrent toxicity. Thus, in significant meprobamate ingestion, orogastric lavage with a large-bore tube and multiple-dose activated charcoal may be indicated. Whole-bowel irrigation might be helpful if multiple pills or small concretions are noted.

Bromides

Although pharmaceutical bromides have largely disappeared from the US pharmacopeia, bromide toxicity still occurs because of the availability of bromide salts of common drugs, such as dextromethorphan. Bromide has a long plasma half-life (12 days) and toxicity typically occurs over a period of time, as tissue concentrations increase. Bromide salts are irritating to the GI tract. Chronic use of bromides can lead to dermatologic changes, with the hallmark characteristic of a facial acneiform rash. A spurious hyperchloridemia may be found as a result of the interference of bromide with the chloride assay on older analyzers (Chap. 17).

Zolpidem/Zaleplon/Eszopiclone

These agents have supplanted benzodiazepines as the most commonly prescribed hypnotics. Although zolpidem and zaleplon are structurally unrelated to the benzodiazepines, they bind preferentially to a benzodiazepine receptor subtype in the brain. In isolated overdoses, drowsiness and CNS depression are common, but coma and respiratory depression are exceptionally rare. Flumazenil can reverse the effects of these drugs.

Propofol

Propofol is a rapidly acting intravenous sedative-hypnotic used for either the induction or maintenance of general anesthesia. Propofol is highly lipid solu-

ble and crosses the blood–brain barrier rapidly. Onset of anesthesia usually occurs in less than 1 minute with a duration of action lasting 3–8 minutes because of its rapid redistribution from the central nervous system.

Propofol use is associated with various adverse outcomes. Acutely, propofol causes dose-related respiratory depression; transient apnea may occur. Prolonged infusions of longer than 48 hours at rates of 5 mg/kg/h are associated with lactic acidosis and cardiac and skeletal muscle injury. The unique nature of the carrier base, a milky soybean emulsion formulation, is associated with impaired macrophage function and hypertriglyceridemia.

Etomidate

Etomidate is a nonbarbiturate, intravenous hypnotic primarily used for anesthesia induction. The onset of action is less than 1 minute and its duration is less than 5 minutes.

The 35% propylene glycol diluent has been implicated in the development of a hyperosmolar metabolic acidosis. Involuntary muscle movements are common during induction. Etomidate depresses adrenal production of cortisol and aldosterone even rarely after a single dose.

Flumazenil

HISTORY

Attempts to produce benzodiazepines with potent anxiolytic and anticonvulsant activity and diminished sedative and muscle-relaxing properties resulted in derivatives that had high in vitro binding affinities but lacked in vivo activity. An inability to enter the central nervous system was considered an explanation for this discordance. During an experiment that attempted to demonstrate CNS penetration for these derivatives, it was noted that when diazepam was given to incapacitate the animals, it surprisingly had a very weak effect. This lack of potency, followed by further modifications, led to the synthesis of flumazenil a benzodiazepine antagonist.

PHARMACOLOGY

Flumazenil is a competitive antagonist at the benzodiazepine receptor with very weak agonist properties in animal models and in humans. The benzodiazepine receptor modulates the effect of γ-aminobutyric acid (GABA) on the $GABA_A$ receptor by increasing the frequency of opening of the Cl^- channel, leading to hyperpolarization. Agonists such as diazepam stimulate the benzodiazepine receptor; inverse agonists stimulate the benzodiazepine receptor and result in the opposite effects; and antagonists, such as flumazenil, competitively occupy the benzodiazepine receptor without causing any functional change and without allowing an agonist or inverse agonist access to the receptor. Positron emission tomography (PET) investigations reveal that 1.5 mg of flumazenil leads to an initial receptor occupancy of 55%, whereas 15 mg of flumazenil causes almost total blockade of benzodiazepine receptor sites. Table A21–1 summarizes the pharmacokinetic properties of flumazenil.

Effects with Therapeutic Benzodiazepine Dosing

Volunteer studies demonstrate the ability of flumazenil to reverse the effect of benzodiazepines. Reversal is dose dependent and begins within several minutes, with peak effects occurring within 6–10 minutes. Most individuals achieve complete reversal of benzodiazepine effect with a total IV dose of 1 mg. When a benzodiazepine is given to achieve conscious sedation during a procedure, flumazenil appears safe and effective in the reversal of sedation and the partial reversal of amnesia and cognitive impairment. Resedation occurs within 20–120 minutes, depending on the dose and pharmacokinetics of the benzodiazepine, as well as the dose of flumazenil. For this reason, patients must be carefully monitored, and subsequent doses of flumazenil given as needed.

Paradoxical reactions to benzodiazepines are uncommon. The mechanism is unclear and has been attributed to a disinhibition reaction. Management strategies include administering higher doses of the benzodiazepines, adding other agents such as opioids or droperidol, stopping the procedure, or using flumazenil. Flumazenil, 0.5 mg IV, abolished paradoxical reactions in patients undergoing endoscopy.

TABLE A21–1. Physicochemical and Pharmacologic Properties of Flumazenil

pK_a	Weak base
Partition coefficient at pH 7.4	14 (octanol/aqueous PO_4 buffer)
Volume of distribution	1.06 L/kg
Distribution half-life ($t_{1/2}\alpha$)	≤ 5 minutes
Metabolism	Hepatic: three inactive metabolites High clearance
Elimination	First order
Protein binding	54–64%
Elimination half-life ($t_{1/2}\beta$)	53 minutes
Onset of action	1–2 minutes
Duration of action	Dependent on dose and elimination of benzodiazepine, time interval, dose of flumazenil, and hepatic function

Flumazenil has not consistently reversed benzodiazepine-induced respiratory depression. When patients with respiratory depression from IV midazolam were studied, flumazenil awakened patients rapidly, but failed to affect minute ventilation and had little effect on oxygen saturation. Thus benzodiazepine-induced hypoventilation should be managed with standard procedures such as supplemental oxygen, airway stabilization, bag-valve-mask ventilation, and endotracheal intubation, if indicated.

Use in the Overdose Setting

The use of flumazenil following overdose has provoked substantial controversy. The first argument against its use is that benzodiazepines rarely cause morbidity and mortality. Proponents of flumazenil suggest that although it may not save lives, it reduces unnecessary diagnostic testing. Low-risk patients are likely to benefit from the use of flumazenil. Classification of overdosed comatose patients can help define indications of flumazenil use. Low-risk patients have CNS depression with normal vital signs, no other neurologic findings, no evidence of ingestion of a tricyclic antidepressant by history or electrocardiogram (ECG), no seizure history, and absence of an available history of chronic benzodiazepine ingestion. All other patients are considered high risk. When low-risk patients are treated with flumazenil, awakening without adverse effects generally results. In high-risk patients, awakening is often incomplete and seizures may result. Unfortunately most overdosed patients are in the high-risk group. Therefore, selected and infrequent use may have clinical benefits, but routine use is inadvisable.

Adverse Effects and Safety Issues

Although flumazenil has been used safely in volunteers and following conscious sedation, concerns over the precipitation of seizures in benzodiazepine-dependent patients, the unmasking of dysrhythmias in patients with coingestion of a prodysrhythmic drug, and resedation significantly limit its use. Although these adverse effects are uncommon, they must be considered in relationship to the benefits of flumazenil. A consensus report suggested that (a) flumazenil is not a substitute for primary emergency care; (b) hypoxia and hypotension should be corrected before flumazenil is used; (c) small titrated doses of flumazenil should be used; (d) flumazenil should be avoided in patients with a history

of seizures, evidence of seizures or jerking movements, or evidence of a cyclic antidepressant overdose; and (e) flumazenil should not be used by inexperienced clinicians. It is possible that, if doses are kept small (<1 mg), enough of the benzodiazepine receptor may remain occupied so that abrupt withdrawal and seizures are uncommon.

Flumazenil is best avoided in the overdose setting when there is evidence that a drug capable of causing seizures or dysrhythmias was ingested. Any indication that theophylline, carbamazepine, chloral hydrate, chloroquine, and/or chlorinated hydrocarbons were ingested is a contraindication to the use of flumazenil. When there is a suggestion, based on history, clinical findings, or ECG findings (prolonged QRS complex or prolonged QTc interval) that a cyclic antidepressant is involved, flumazenil should not be used. In the event of flumazenil-induced seizures, a therapeutic dose of a benzodiazepine such as diazepam or lorazepam should be effective.

Dosing

Slow IV titration (0.1 mg/min) to a total dose ≤1 mg seems most reasonable. Resedation may occur at 20–120 minutes, and it may be necessary to readminister flumazenil. Although not FDA approved, a continuous intravenous infusion in saline or dextrose of 0.1–1.0 mg/h has been employed following the loading dose.

Availability

Flumazenil is available in a concentration of 0.1 mg/mL, with parabens in 5-mL and 10-mL vials.

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73 Amphetamines

Amphetamine is the common name and acronym for racemic β-phenylisopropylamine or α-methylphenylethylamine and belongs in the family of phenylethylamines. Numerous substitutions of the phenylethylamine structure are possible, resulting in different amphetaminelike compounds. Commonly, these compounds are referred to as amphetamines or amphetamine analogs, although the term phenylethylamines is more precise. Amphetamines have been advocated by the medical communities for the treatment of depression, obesity, enuresis, postencephalitic Parkinsonism, coma, and alcoholism. The few medical indications for amphetamines are narcolepsy, attention deficit hyperactivity disorder, and short-term weight reduction. The prescriptive amphetamines include methylphenidate, pemoline, phentermine, phendimetrazine, amphetamine, dextroamphetamine, and methamphetamine.

In the 1980s, the so-called designer amphetamines, such as methylenedioxymethamphetamine (MDMA), were popularized, resulting in the amendment of the Controlled Substances Act by what became known as the "designer drugs" laws. Although this prospectively illegalized derivatives of amphetamine, MDMA remains a drug that is widely used by college students and partygoers. The 1990s saw a dramatic resurgence of methamphetamine abuse, spread throughout much of the United States. Today, methamphetamine is the most common illicit drug produced by clandestine laboratories.

PHARMACOLOGY

The pharmacologic effects of amphetamines are complex but the primary mechanism of action is the release of catecholamines, particularly dopamine and norepinephrine, from the presynaptic terminals. Two storage pools exist for dopamine in the presynaptic terminals: the vesicular pool and the cytoplasmic pool. The vesicular storage of dopamine and other biogenic amines is maintained by the acidic environment inside the vesicles and the persistence of a stabilizing electrical gradient with respect to the cytoplasm. Amphetamines release catecholamines from the cytoplasmic pool by exchange at the uptake transporter site on the neuronal and vesicular membrane. At high doses, an additional mechanism is invoked, as amphetamines diffuse through the cellular and vesicular membranes, alkalinizing the vesicles, permitting biogenic amine release from the vesicles and delivery into the synapse by reverse transport. Binding selectivity to the neurotransmitter transporters largely determines the range of pharmacologic effects for the particular amphetamine. Because MDMA affinity for serotonin transporters is 10 times greater than dopamine and norepinephrine transporters, it produces primarily serotonergic effects. Because amphet-

amines directly interact with neurotransmitter transporters, minor modification of the molecule may significantly alter its pharmacologic profile.

PHARMACOKINETICS AND TOXICOKINETICS

In general, amphetamines are relatively lipophilic and hence they can cross the blood–brain barrier readily. They have large volumes of distribution. Amphetamines differ structurally from catecholamines in that they lack the catechol structure (hydroxyl groups at the 3 and 4 positions of the phenyl ring) and are resistant to metabolism by catechol-*O*-methyl transferase (COMT). The addition of an α-methyl group in amphetamines confers resistance to metabolism by monoamine oxidase enhancing oral bioavailability. These characteristics permit better oral bioavailability and longer duration of effects.

Amphetamines are eliminated via multiple pathways, including diverse routes of hepatic transformation and by renal elimination. Increased amphetamine toxicity is a potential concern in patients with decreased CYP2D6 activity, although because multiple enzymes and pathways (including renal) are involved in amphetamine elimination, increased toxicity is unlikely.

CLINICAL MANIFESTATIONS

The clinical effects of amphetamines are largely related to the stimulation of central and peripheral adrenergic receptors. These clinical manifestations and complications are similar to those from cocaine use and may be indistinguishable except for the duration of effect of amphetamines, which tends to be longer (up to 24 hours).

Compared to cocaine, amphetamines are less likely to cause seizures, dysrhythmias, and myocardial ischemia. This may be related to the sodium channel blocking and thrombogenic effects of cocaine. Psychosis appears to be more likely with amphetamines than cocaine, which may be related to the more prominent dopaminergic effects of amphetamines. Tachycardia and hypertension are the most common manifestations of cardiovascular toxicity. Most patients present to the emergency department, however, because of the CNS manifestations. These patients are anxious, volatile, aggressive, and may have life-threatening agitation. Visual and tactile hallucinations, as well as psychoses, are common. Other sympathetic findings include mydriasis, diaphoresis, and hyperthermia. Death from amphetamine toxicity most commonly results from hyperthermia, dysrhythmias, and intracerebral hemorrhage. Tachycardia, hypertension, and vasospasm may lead to cerebral infarction, myocardial infarction, and related complications. Agitation, increased muscular activity, and hyperthermia can result in metabolic acidosis and rhabdomyolysis

Amphetamine users seeking intense “highs” may go on “speed runs” for days to weeks. Because of the development of acute tolerance, they use increasing amounts of amphetamines during these periods, usually without much sustenance or sleep, attempting to achieve their desired euphoria. Acute psychosis resembling paranoid schizophrenia may occur during these binges, and has contributed to both amphetamine-related suicides and homicides.

Other effects include repetitive behavior patterns, picking at the skin, bruxism, and choreoathetoid movements. Necrotizing vasculitis and cardiomyopathy are also associated with amphetamine abuse. Pulmonary hypertension and valvular heart disease is also associated with the use of the appetite-suppressant amphetamines, such as fenfluramine.

In experimental animals, the chronic administration of many amphetamines, particularly MDMA and its analogs, depletes dopamine and serotonin in the neuronal synapses and produces irreversible destruction of those neurons.

DIAGNOSTIC TESTING

There is no readily available drug-specific serum analysis. Qualitative urine immunoassay testing for amphetamines is available, but it is not valuable in the acute overdose setting. Both false-positive and false-negative results are common. Many cold preparations contain structurally similar substances (such as pseudoephedrine) that can cross-react with the immunoassay. Even a true-positive result only means that the patient has used an amphetamine analog within the last several days. Immunoassays do not react with all amphetamines, resulting in false-negative results. The gold standard for drug testing, gas chromatography–mass spectrometry analysis, can misidentify isomeric substances such as *l*-methamphetamine, which is present in nasal inhalers, with *d*-methamphetamine, if performed by inexperienced personnel.

Blood specimens should be sent for glucose, BUN, and electrolyte assays. Hyponatremia should be considered for patients with altered sensorium and suspected MDMA usage. An ECG should be obtained to exclude ischemia, hyperkalemia, and cardiac toxicity, and continuous cardiac monitoring should be initiated. A complete blood count, urinalysis, coagulation profile, chest radiograph, CT of the head, and lumbar puncture may be necessary, depending on the clinical presentation.

MANAGEMENT

Table 73–1 summarizes the therapeutic approach to a patient with amphetamine toxicity. The initial medical assessment of the agitated patient must include the vital signs and a rapid complete physical examination. An often-neglected vital sign is the rectal temperature. Hyperthermia, a frequent and rapidly fatal manifestation in patients with drug-induced delirium, requires immediate interventions to achieve cooling.

The most appropriate choice of sedation is a benzodiazepine because of the group's high therapeutic index and good anticonvulsant activity. The benzodiazepines are effective for the treatment of delirium induced by acute overdose of cocaine, amphetamines, and other comparable drugs, and the delirium associated with ethanol and sedative-hypnotic withdrawal. Although others recommend antipsychotic agents, the benzodiazepines appear to be equally efficacious and safer in the management of acute amphetamine toxicity.

INDIVIDUAL AGENTS

Methamphetamine

Methamphetamine is referred to as "crack," "speed," "yaba," and "go." The pharmacologic profile of methamphetamine is quite similar to amphetamine, although the effects on the central nervous system are more substantial. "Ice," the common name for methamphetamine in the 1990s because of its crystal form, does not differ pharmacologically from other forms of methamphetamine. Because of a prolonged half-life of 19–34 hours, the duration of its acute effects can be greater than 24 hours.

Methamphetamine is easily synthesized with the proper chemicals and minimal equipment. The primary ingredient of methamphetamine synthesis

TABLE 73–1. Management of Patients with Amphetamine Toxicity

Agitation
Benzodiazepines (usually adequate for the cardiovascular manifestations)
Diazepam 10 mg (or equivalent) IV, repeat rapidly until the patient is calm (cumulative dose may be >100 mg of diazepam)

Seizures
Benzodiazepines
Barbiturates
Propofol

Hyperthermia
External cooling
Control agitation rapidly

Gastric decontamination and elimination
Activated charcoal for oral ingestions

Hypertension
Control agitation first
α-Adrenergic receptor antagonist (phentolamine)
Vasodilator (nitroprusside, nitroglycerin)

Delirium or hallucinations with abnormal vital signs
If agitated: benzodiazepines

Delirium or hallucinations with normal vital signs
Consider haloperidol or droperidol (consider risk/benefit)

is ephedrine. Nonprescription sales of pseudoephedrine are now restricted and monitored in many states. Lead acetate, which is used as a substrate for the reaction, can result in epidemic lead poisoning.

3,4-Methylenedioxymethamphetamine

MDMA is commonly known as "ecstasy," "E," "Adam," and "XTC." Structural relatives include 3,4-methylenedioxyethamphetamine (MDEA; "Eve") and methylenedioxyamphetamine (MDA; "love drug"), and MDMA-related substances include 2CB (4-bromo-2,5-methoxyphenylethylamine), 2,4-dimethoxy-4-(*n*)-propylthiophenylethylamine (2C-T7), and *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB) (Table 73–2). The term *ecstasy* can be used for all of these substances. Typically, MDMA is available in colorful and branded tablets, ranging from 50–200 mg. MDMA and similar analogs are so-called entactogens (meaning touching within), capable of producing euphoria, inner peace, and a desire to socialize. People who use MDMA report that it enhances pleasure, heightens sexuality, and expands consciousness without the loss of control. Negative effects reported with acute use include ataxia, restlessness, confusion, poor concentration, and memory problems. MDMA is a potent stimulus for the release of serotonin. The sympathetic effects of MDMA are mild in low doses. However, when a large amount of MDMA is taken, the clinical presentation is similar to that of other amphetamines and death can result from similar complications. Significant hyponatremia has been reported with MDMA use, and is caused by release of vasopressin (antidiuretic hormone [ADH]). Furthermore, consequential water intake combined with sodium loss from physical exertion (in dance clubs)

TABLE 73–2. Designer Amphetamines

Xenobiotic	Clinical Characteristics
4-Bromo-2,5-dimethoxy-amphetamine (DOB)	Marked psychoactive effect potency >mescaline Sold as impregnated paper, like LSD Delayed onset of action, peak 3–4 h Fantasy, mood altering for 10 h, resolution 12–24 h Agitation, sympathetic excess
4-Bromo-2,5-methoxyphenyl-ethylamine (2CB, MFT)	Relaxation Sensory distortion Agitation Hallucination Potency >mescaline
Methcathinone (cat, Jeff, Khat, ephedrone)	Comparable to hallucinogenic and sympathetic effects of methamphetamine
4-Methyl-2,5-dimethoxyamphetamine (DOM/STP) (serenity, tranquility, peace)	Narrow therapeutic index Euphoria, perceptual distortion Hallucinations, sympathetic stimulation
3,4-Methylenedioxyamphetamine (MDA, love drug)	Empathy, euphoria Agitation, delirium, hallucinations, death associated with sympathetic excess
3,4-Methylenedioxyethamphetamine (MDEA, Eve)	Comparable to MDMA Sympathetic excess
3,4-Methylenedioxymethamphetamine (MDMA, Adam, ecstasy, XTC)	Psychotherapy “facilitator” Euphoria, empathy Nausea, anorexia Anxiety, insomnia Sympathetic excess
para-Methoxyamphetamine (PMA)	Potent hallucinogen Marked stimulant effect
2,4,5-Trimethoxyamphetamine	Similar to mescaline

may be crucial to the development of hyponatremia. A major concern with MDMA usage is its long-term effects on the brain.

Khat, Cathinone, and Methcathinone

Khat (also known as quat and gat), the fresh leaves and stems from the *Catha edulis* shrub, is one of the most commonly used drugs in eastern and central Africa, and in parts of the Arabian peninsula. The leaves and the tender stems are chewed, or occasionally concocted into tea, and used at social gatherings in these countries. The primary active ingredient in fresh leaves is cathinone (benzylketoamphetamine). As the leaves age, cathinone is degraded into cathine, which explains why dried khat is neither popular nor widely distributed.

Methcathinone, the methyl derivative of cathinone, is chemically synthesized from ephedrine. The potency of methcathinone is comparable to that of methamphetamine. Methcathinone—also termed ephedrone, or sold under the street names of “cat” or “Jeff”—currently remains widely abused in Russia.

Ephedrine or Ma-Huang Herbal Products

Ephedrine was commonly found in nonprescription cold preparations. Ephedrine is the active substance in the Chinese plant ma-huang, which has been used for centuries for the treatment of asthma. Although ephedrine is much

less potent than amphetamine, when combined with other catecholamine-stimulating xenobiotics, or when taken in large quantities, significant toxicity can occur. Herbal products with *Citrus aurantium* (bitter orange) contain a number of adrenergic amines, including synephrine, and have supplanted ephedra products. *Citrus aurantium* has similar pharmacologic effects and toxicity as ephedra.

74 | Cocaine

HISTORY AND EPIDEMIOLOGY

Cocaine is a natural alkaloid contained in the leaves of *Erythroxylum coca,* a shrub that grows abundantly in Colombia, Peru, Bolivia, the West Indies, and Indonesia. As early as the 6th century, the inhabitants of Peru chewed or sucked on the leaves for social and religious reasons. In the 1100s, the Incas used cocaine-filled saliva as local anesthesia for ritual trephinations of the skull. Europeans knew little about cocaine until 1884, when cocaine was introduced as a local anesthetic for eye surgery. By 1887 more than 30 cases of severe toxicity were reported, and by 1895 at least 8 fatalities were reported.

Recreational cocaine use was legal in the United States until 1914, when it was restricted to medical professionals. It was not until 1982, however, that the first cocaine-associated myocardial infarction was reported in the United States. Recent estimates suggest that almost 34 million Americans have used cocaine at least once, with just over 2.0 million being current regular users.

PHARMACOLOGY

Cocaine hydrochloride can be insufflated or applied to other mucous membranes, dissolved in water and injected, or ingested, but it rapidly degrades during pyrolysis. Smokeable cocaine (crack) is formed by dissolving cocaine hydrochloride in water and adding a strong base. A hydrocarbon solvent is added, the cocaine base is extracted into the organic phase, and then evaporated. The term *free-base* refers to the use of cocaine base in solution.

Cocaine is rapidly absorbed following all routes of exposure; however, when applied to a mucous membrane or ingested, its vasoconstrictive properties slow the rate of absorption and delay the peak effect. Whereas bioavailability exceeds 90% with intravenous and smoked cocaine, it is only approximately 80% following nasal application. Table 74–1 lists the typical onsets and durations of action for various routes of cocaine use.

Following absorption, cocaine is approximately 90% bound to plasma proteins and its volume of distribution is about 2.7 L/kg. The terminal elimination half-life of cocaine is on the order of 1 hour. Cocaine is metabolized by multiple enzymatic and nonenzymatic routes. Benzoylecgonine (BE), which is formed by nonenzymatic hydrolysis, is the principle metabolite analyzed in urine screens for cocaine use. Another pathway uses plasma cholinesterase (pseudocholinesterase) and may account for interindividual variability in response to cocaine. A unique metabolite anhydroecgonine methyl ester (AEME) or methylecgonine results only from smoked cocaine. Finally, ethanol interacts with cocaine in a transesterification reaction to produce benzoylethylecgonine, which is also called ethyl cocaine or cocaethylene.

PATHOPHYSIOLOGY

General Effects

Cocaine blocks the reuptake of biogenic amines. Specifically, these effects are described for serotonin and the catecholamines dopamine, norepinephrine, and epinephrine. Dopamine excess produces psychomotor agitation, whereas tachy-

TABLE 74–1. Pharmacology of Cocaine

Route of Exposure	Onset of Action (min)	Peak Action (min)	Duration of Action (min)
Intravenous	<1	3–5	30–60
Nasal insufflation	1–5	20–30	60–120
Smoking	<1	3–5	30–60
Gastrointestinal	30–60	60–90	Unknown

cardia emanates from adrenally-derived epinephrine, and hypertension results from neuronally derived norepinephrine. Serotonin is an important modulator of dopamine and has a role in cocaine addiction, reward, and seizures.

Additionally, cocaine increases excitatory amino acid concentrations in the brain, which cause agitation and seizures.

Specific Organ Pathophysiology

Atherogenesis, Coagulation, and Ischemic Cardiac Events

Cocaine use is associated with cardiac ischemia and infarction in young people, and may account for as many as 25% of myocardial infarctions in patients ≤45 years old. In addition to increasing myocardial oxygen demand, vasoconstriction, the simultaneous use of nicotine, enhanced atherogenesis, and procoagulant effects are all important determinants of ischemia.

Dysrhythmias

Cocaine blocks cardiac sodium channels responsible for phase 0 depolarization of the cardiac action potential. Thus cocaine can be characterized as a Vaughn-Williams type IA antidysrhythmic. Another effect of sodium channel blockade, the Brugada pattern, is also associated with cocaine use. Cocaine also blocks cardiac potassium channels resulting in QTc prolongation and torsades de pointes.

Pulmonary

Smoked cocaine induces or exacerbates asthma. While it is possible that bronchospasm results from direct administration of cocaine to the airways, inhaled contaminants of cocaine, or thermal insult, AEME (the unique pyrolytic metabolite of cocaine that acts as a muscarinic agonist) produces bronchospasm in experimental animals.

CLINICAL MANIFESTATIONS

Vital sign abnormalities are characteristic of the sympathomimetic toxidrome. Hypertension, tachycardia, tachypnea, and hyperthermia can all occur. Experimental and clinical evidence suggests that hyperthermia is the most critical vital sign abnormality. Additional sympathomimetic findings include mydriasis, diaphoresis, and neuropsychiatric manifestations.

Cocaine produces end-organ toxicity in virtually every organ system in the body. These events result from vasospasm, hemorrhage secondary to increased vascular sheer force (dP/dT), or enhanced coagulation.

Central Nervous System

Seizures, coma, headache, focal neurologic signs or symptoms, or behavioral abnormalities that persist longer than the predicted duration of effect of cocaine

should alert the clinician to a potential catastrophic adverse CNS event. Hemorrhage can occur at any anatomical site in the CNS. Subarachnoid, intraventricular, and intraparenchymal bleeding are all well described in association with cocaine use. Both vasospastic (bland) infarction and transient ischemic attack (TIA) are also reported. Vasospasm also can injure the spinal cord, resulting in paralysis from an anterior spinal artery syndrome.

Eyes, Nose, and Throat

Sympathetic excess produces mydriasis through stimulation of the dilator fibers of the iris. The pupils characteristically retain their ability to respond to light. Like other pupillary dilators, cocaine can produce acute angle-closure glaucoma. Vasospasm of the retinal vessels can produce both unilateral and bilateral loss of vision. Following both intentional and unintentional application of cocaine to the eye, the superficial corneal layer is shed, resulting in pain and decreased acuity. The loss of eyebrow and eyelash hair from thermal injury associated with smoking crack cocaine is called madarosis.

Chronic cocaine use can produce perforation of the nasal septum. This finding most likely results from repeated ischemic injury with resultant tissue loss. Angioedema and oropharyngeal burns are associated with smoking crack cocaine. These effects are mostly likely the result of inhaling superheated fumes.

Pulmonary

Pneumothorax, pneumomediastinum, and pneumopericardium are reported following both intranasal cocaine use and smoking crack. These findings do not represent direct drug toxicity, but rather result from increased intrathoracic pressure while breath holding.

Cocaine use exacerbates reactive airway disease and it is common for patients to present with shortness of breath and wheezing. Another cause for cough and shortness of breath has been termed “crack lung,” which refers to hemorrhagic alveolitis resulting from cocaine use. Finally, vasospasm and subsequent thrombosis of the pulmonary artery or its branches can produce pulmonary infarction.

Cardiovascular

Chest pain or discomfort is a common emergency department complaint in cocaine users, although only approximately 5% of patients with complaints referable to the heart manifest biochemical evidence of myocardial injury. Entities to consider include the pulmonary and esophageal etiologies described above, referred abdominal symptoms (see below), chest wall injury, aortic dissection, coronary artery dissection, and dysrhythmias. No single sign or symptom, or combination of signs and symptoms, reliably identifies cardiovascular injury from among those discussed in the differential diagnosis. Chronic cocaine use is associated with a dilated cardiomyopathy.

Abdominal

Cocaine users have a disproportionate incidence of perforated ulcers. Vasospasm produces ischemic colitis that can present with abdominal pain or bloody stools. More severe or persistent vasospasm with or without thrombosis can lead to intestinal infarction with attendant hypotension and metabolic acidosis. Signs and symptoms of bowel obstruction, such as vomiting or dis-

tension, might suggest body packing (gastrointestinal drug smuggling; see below). Although less common, splenic and renal infarctions can also occur.

Musculoskeletal

Rhabdomyolysis is common. Unlike most other toxicologic disorders, however, psychomotor agitation is not a prerequisite for cocaine-associated rhabdomyolysis. Muscle injury may result from vasospasm or direct muscle toxicity.

Neuropsychiatric

Low-dose administration produces alertness, exhilaration, hypersexual behavior, and other "desired" effects. These effects rarely bring patients to healthcare. As the cocaine dose increases, agitation, aggressive behavior, confusion, disorientation, and hallucinations can develop. Other manifestations include a variety of movement disorders such as acute dystonias or choreoathetoid movements that are also termed "crack-dancing." Following binge use of cocaine, a "washed-out" syndrome occurs that is best described by dopamine depletion. Although patients complain of anhedonia and desire to sleep, they are arousable and remain cognitively intact.

Obstetrical

Acute cocaine use during pregnancy is associated with abruptio placenta, causing patients to present with abdominal pain and vaginal bleeding. Chronic use is associated with low birth weight and nonspecific morphologic abnormalities.

DIAGNOSTIC TESTING

Cocaine and its principal metabolite (benzoylecgonine) can be detected in blood, urine, saliva, hair, and meconium. Although cocaine is rapidly eliminated within just a few hours of use, benzoylecgonine is easily detected in the urine for 2–3 days following last use.

The greatest use for cocaine testing is in cases of unintentional poisoning or suspected child abuse and neglect. Here confirmation of a clinical suspicion is essential to support a legal argument. In addition, there may be some usefulness to urine testing of body packers, especially when the concealed substance is unknown. Also, conversion from a negative study on admission to a positive study not only confirms the substance ingested, but also suggests packet leakage, which could be a harbinger of life-threatening toxicity. One final indication for urine testing for cocaine is in young patients with chest pain syndromes where the history of drug use is not forthcoming.

In the setting of cocaine-associated chest pain, the ECG has neither the sensitivity nor the specificity necessary to permit exclusion or confirmation of cardiac injury. Consequently, cardiac markers are always required adjuncts when considering myocardial ischemia or infarction. A chest radiograph may be useful to exclude certain etiologies in patients with chest discomfort, or to identify free air under the diaphragm when gastrointestinal perforation is suspected.

MANAGEMENT

General Supportive Care

As in the case of all poisoned patients, the initial emphasis must be on stabilization and control of the patient's airway, breathing, and circulation. If intubation

is required, it is important to recognize that cocaine toxicity may be a relative contraindication to the use of succinylcholine. Specifically, in the setting of rhabdomyolysis, hyperkalemia may be exacerbated by succinylcholine administration, and life-threatening dysrhythmias may result. Additionally, because plasma cholinesterase (PChE) metabolizes both cocaine and succinylcholine, either prolonged cocaine toxicity or paralysis, or both, may result. Hypotension should be treated with intravenous 0.9% sodium chloride solution, as many patients are volume depleted from diaphoresis and hyperthermia.

Because hyperthermia is a critical vital sign abnormality, immediate, rapid cooling with ice-water immersion or the combined use of mist and fan is required to normalize body temperature. Antipyretics (acetaminophen or salicylates), medications that prevent shivering (chlorpromazine or meperidine), and dantrolene are not indicated because they are inefficient or ineffective and have the potential for adverse drug events.

Either a rapid reagent glucose test should be obtained, or hypertonic dextrose should be empirically administered to patients with altered mental status. Sedation with a benzodiazepine remains the mainstay of therapy. The pharmacokinetics of midazolam and diazepam are superior to lorazepam for this indication. Initial dosing should be consistent with routine practices and increased incrementally as needed. For example, if using diazepam, the starting dose might be 5–10 mg, which can be repeated every 3–5 minutes and increased if necessary. Large doses of benzodiazepines may be necessary (on the order of 1 mg/kg of diazepam). If benzodiazepines fail to achieve adequate sedation, either a rapidly acting barbiturate or propofol should be administered. Phenothiazines and butyrophenones are contraindicated.

Hypertension and tachycardia usually respond to sedation, cooling, and volume resuscitation. In the uncommon event that hypertension and/or tachycardia persist, the use of a β-adrenergic antagonist or a mixed α- and β-adrenergic antagonist are absolutely contraindicated. A direct-acting vasodilator (such as nitroglycerin or nitroprusside) or an α-adrenergic antagonist (such as phentolamine) may be considered.

Decontamination

The majority of patients who present to the hospital following cocaine use will require no gastrointestinal decontamination. Patients who ingest cocaine in an attempt to conceal evidence during an arrest (body stuffing) or who transport large quantities of drug across international borders (body packing) may require aggressive decontamination, possibly including surgery.

Specific Management

End-organ manifestations of vasospasm that do not resolve with sedation, cooling, and volume resuscitation should be treated with a vasodilator (such as phentolamine). When possible, it is preferable to deliver direct intraarterial administration of phentolamine into the affected vascular bed. Because this approach is not always feasible, systemic therapy is indicated. Phentolamine can be dosed intravenously in increments of 1–2.5 mg, repeated as necessary, until symptoms resolve or systemic hypotension develops.

Acute Coronary Syndrome

High-flow oxygen therapy may overcome some of the supply–demand mismatch that occurs with coronary insufficiency. Because cocaine induces plate-

let aggregation, it is reasonable to administer aspirin. In addition, there is probably a role for administration of morphine, as it relieves cocaine induced vasoconstriction and offers the same theoretical benefits that it provides in patients with atherosclerotic heart disease (ASHD). Nitroglycerin reduces cocaine-induced coronary vasoconstriction of both normal and diseased vessels, and relieves chest pain and associated symptoms in patients with cocaine-associated chest pain. However, in clinical trials, benzodiazepines are as effective as, or superior to nitroglycerin.

β-Adrenergic antagonism increases lethality in cocaine-toxic animals; in humans, it exacerbates cocaine-induced coronary vasoconstriction and produces severe paradoxical hypertension. Similarly, with regard to coronary constriction, labetalol is no better than placebo. Thus in the setting of cocaine use, β-adrenergic antagonism is absolutely contraindicated. Phentolamine may be considered if vasospasm persists. If tachycardia is clinically significant, diltiazem can be administered and titrated to effect as long as the tachycardia is not compensatory for a low cardiac output that results from global myocardial dysfunction.

There are no data on the use of either unfractionated or low-molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, or clopidogrel. The decision whether or not to use any of these agents should be based on a risk-to-benefit analysis. When acute thrombosis is likely, thrombolytic therapy should be considered, as long as the patient's blood pressure, mental status, and the possibility of aortic dissection are considered. Although the numbers of patients treated with thrombolytic therapy are insufficient to demonstrate efficacy in terms of mortality, evidence of revascularization is encouraging. However, it is preferable to provide a mechanical approach to revascularization, especially given the fact that spasm may be a fairly common etiology of cocaine-induced infarction.

Dysrhythmias

Most patients present for healthcare with sinus tachycardia that resolves following sedation, cooling, rehydration, and time to metabolize the drug. However, cocaine use is associated with atrial, supraventricular, and ventricular dysrhythmias, some of which may require additional pharmacotherapy. Wide-complex tachycardias that result from sodium channel blockade should be treated with hypertonic sodium bicarbonate (see Antidotes in Brief: Sodium Bicarbonate). When hypertonic sodium bicarbonate fails to treat the dysrhythmia, lidocaine may be used. Here both β-adrenergic antagonism and the use of type IA and IC antidysrhythmics are absolutely contraindicated. Amiodarone is essentially unstudied in the setting of cocaine toxicity and cannot be recommended at this time. For rapid atrial fibrillation and narrow complex reentrant tachycardias, a calcium channel blocker such as diltiazem is preferred.

Disposition

Patients who present to healthcare facilities with classic sympathomimetic signs and symptoms that resolve spontaneously or with minimal sedation and no signs of end-organ damage can be safely discharged after short periods of observation. Once hyperthermia, rhabdomyolysis, or other signs of end-organ damage are evident, hospital admission is usually required.

For patients with chest pain, a specific management algorithm has been derived based on substantial clinical experience. Those patients with clearly di-

agnostic or evolving ECGs suggestive of ischemia or infarction, positive cardiac markers, dysrhythmias other than sinus tachycardia, congestive heart failure, or persistent pain require admission. Patients who become pain free and whose ECGs return to normal are candidates for discharge if a single cardiac marker obtained at least 8 hours after the onset of chest pain is negative. It is essential to provide all patients a referral for detoxification, as repeated cocaine use is the greatest risk factor for future cardiovascular complications.

SPECIAL SITUATIONS: BODY PACKERS AND BODY STUFFERS

Cocaine body stuffers ingest drug in an attempt to avoid detection or prosecution. The drug is normally unwrapped or wrapped for extracorporeal transport and therefore often readily available for gastrointestinal absorption. The sensitivity and specificity of diagnostic imaging studies are poor. Decontamination with multiple-dose oral activated charcoal therapy should be sufficient in most cases, as cocaine is very well adsorbed to activated charcoal. If symp-

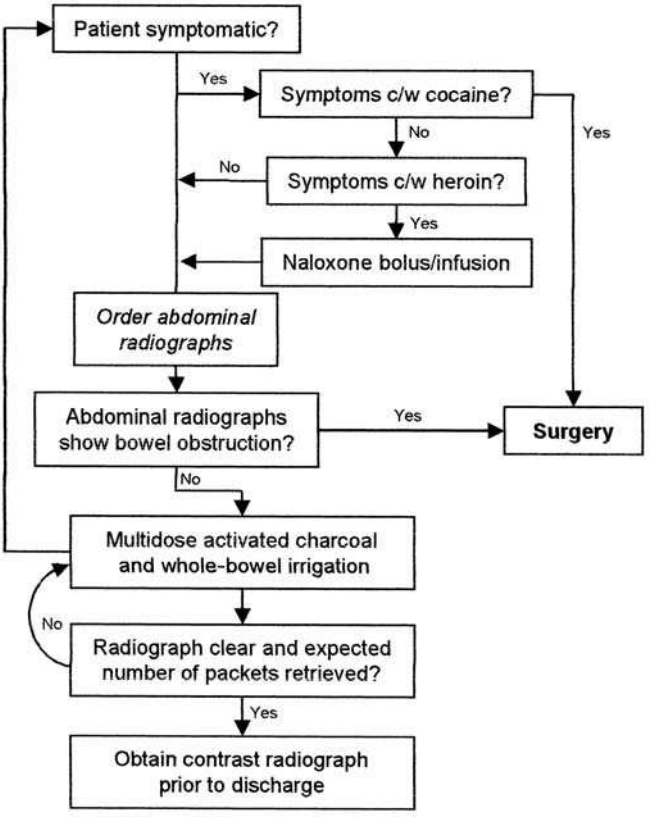

FIG. 74–1. Algorithm for managing cocaine or heroin body packers. c/w = consistent with.

toms of cocaine toxicity develop, they usually manifest within a few hours of ingestion and can be treated as described above.

Body packers ingest large amounts (often 0.5–1 kg) of well-wrapped drug for intracorporeal transport in an attempt to smuggle cocaine across international borders. When packets rupture, the amount of drug per packet exceeds the lethal dose of cocaine. The presence of mechanical bowel obstruction or *any* sign of packet rupture is considered an absolute indication for surgery. In asymptomatic patients whole-bowel irrigation (WBI) with polyethylene glycol electrolyte lavage solution (PEG-ELS) is initiated and dosed in a standard fashion (see Antidotes in Brief: Whole-Bowel Irrigation). Single- or multiple-dose activated charcoal therapy may also be considered. Although it may be beneficial to have activated charcoal in the gut should a packet rupture, activated charcoal can be detrimental if it spills into the peritoneal cavity during surgery. Although plain abdominal radiography may underestimate the number of packets present, it is usually positive initially, and can be used sequentially to assess the efficacy of WBI. When plain abdominal radiography is negative, a confirmatory study should be ordered, such as oral contrast abdominal radiography or a contrast-enhanced CT scan. Because these diagnostic imaging studies are not infallible, it is generally prudent to feed and observe the patient for 24 hours after the chosen study is negative. Figure 74–1 presents an algorithm to clarify these issues.

75 Ethanol

HISTORY AND EPIDEMIOLOGY

Ethanol, or ethyl alcohol, is commonly referred to as alcohol. Ethanol is probably the most commonly used and abused drug in the world. Its use is pervasive among adolescents and adults and among all socioeconomic groups, and represents a tremendous financial and social cost.

In addition to beverages, ethanol is used in hundreds of medicinal preparations as a diluent or solvent in concentrations ranging from 0.3–75%. Mouthwashes may have up to 75% ethanol (150 proof) and colognes typically contain 40–60% ethanol (80–120 proof). These products occasionally cause intoxication, especially when unintentionally ingested by children. Consumption of illicitly produced ethanol ("moonshine") has resulted in methanol, lead, and arsenic poisoning.

The "hangover" syndrome is attributed to congeners, substances that appear in alcoholic beverages in addition to ethanol and water. Congeners contribute to the special characteristics of taste, flavor, aroma, and color of a beverage.

Alcoholism is a leading cause of morbidity and mortality in the United States. The prevalence of alcohol dependence in the United States has been relatively stable, at around 6% for men and 2% for women. The overall estimated annual cost of health expenses related to ethanol is $185 billion. More than 200,000 Americans die annually of alcoholism, far more than those who die of all illicit drugs of abuse combined. Ethanol is the leading cause of mortality in people 15–45 years of age. In ethanol-intolerant individuals, a blood ethanol concentration as low as 20 mg/dL (4.35 mmol/L) impairs driving-related skills. Gross motor control and orientation may be significantly affected at concentrations of 50 mg/dL (10.87 mmol/L). Clinical ethanol intoxication is usually apparent at a blood ethanol concentration of 50 mg/dL (10.87 mmol/L). However, ethanol-tolerant patients may not exhibit impairment even at concentrations greater than 300 mg/dL (65.22 mmol/L).

PHARMACOLOGY

Despite the long history of alcohol use and study, no specific receptor for ethanol has been identified and the mechanism of action leading to intoxication remains the subject of debate. The major actions of ethanol involve enhancing the inhibitory effects of γ-aminobutyric acid (GABA) at $GABA_A$ receptors and blockade of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate, an excitatory amino acid (EAA) receptor. Persistent glycine antagonism and attenuation of glutamatergic neurotransmission by chronic ethanol exposure results in tolerance to ethanol by enhancing EAA neurotransmission and NMDA receptor upregulation. The abrupt withdrawal of ethanol thus produces a hyperexcitable state that leads to the ethanol withdrawal syndrome and excitotoxic neuronal death (Chap. 76).

PHARMACOKINETICS AND TOXICOKINETICS

Ethanol is rapidly absorbed from the gastrointestinal (GI) tract, with approximately 20% absorbed from the stomach and the remainder from the small intestine. Under optimal conditions for absorption, 80–90% of an ingested dose is fully absorbed within 60 minutes, but delayed or decreased absorption is common after eating.

Following complete distribution, ethanol is present in body tissues in a concentration proportional to that of the tissue water content. The concentration in the blood is maintained by back diffusion, which occurs whenever the concentration in the blood falls below that of the tissues. Ethanol freely passes through the placenta, exposing the fetus to ethanol concentrations comparable to that achieved in the mother.

Alcohol dehydrogenase (ADH), the principal enzyme responsible for ethanol oxidation, is an intracellular enzyme that is present in the stomach and the liver. ADH metabolizes ethanol to acetaldehyde, which is then converted to acetate by mitochondrial nicotinamide-adenosine dinucleotide (NAD)-dependent aldehyde dehydrogenase (ALDH). There is a functional polymorphism of the mitochondrial ALDH2 gene that results in impaired acetaldehyde metabolizing capacity that is most prevalent in Pacific Rim Asians. In these people, a small dose of alcohol (0.2 g/kg) causes intense flushing, pronounced cardiovascular and hemodynamic effects, as well as subjective perception of general discomfort. These effects are similar to those induced by disulfiram (Chap. 77), and both prostaglandin antagonists (aspirin) and antihistamines (H_1 and H_2) may attenuate this response.

Ethanol is primarily (>90%) eliminated by the liver via enzymatic oxidation, with 5–10% excreted unchanged by the kidneys, lungs, and sweat. Ethanol is also metabolized via the microsomal ethanol oxidizing system (CYP2E1) located on the endoplasmic reticulum, and the peroxidase-catalase system associated with the hepatic peroxisomes.

ADH is saturated at relatively low blood ethanol concentrations. As the system is saturated, ethanol elimination changes from first-order to zero-order kinetics. In adults, the average rate of ethanol metabolism is 100–125 mg/kg/h in occasional drinkers and up to 175 mg/kg/h in habitual drinkers. As a result, the average-sized adult metabolizes 7–10 g/h and the blood ethanol concentration falls 15–20 mg/dL/h (3.26–4.35 mmol/L/h). Tolerant drinkers, by inducing CYP2E1, may increase their clearance of ethanol to 30 mg/dL/h (6.52 mmol/L/h). Although the average ethanol clearance rate is about 20 mg/dL/h (4.35 mmol/L/h), there is considerable individual variation (standard deviation of about 6 mg/dL/h [1.30 mmol/L/h]) (Table 75–1).

Pharmacodynamics

The most frequent ethanol–drug interactions occur as a result of an ethanol-induced increase in hepatic drug-metabolizing enzyme activity. In contrast, acute ethanol use may inhibit metabolism of other drugs, which may be a result of decreased hepatic enzyme activity or blood flow. The interaction between ethanol and disulfiram (Antabuse) is well described and it can be life-threatening (Chap. 77).

Ethanol has additive sedative effects when ingested with antihistamines, cyclic antidepressants, phenothiazines, opioids, and other sedative-hypnotics such as benzodiazepines, barbiturates, glutethimide, and chloral hydrate (“Mickey Finn”). Ethanol also potentiates the pharmacologic effects of vasodilators and oral hypoglycemics, and may enhance the antiplatelet action of aspirin.

TABLE 75–1. Basic Information and Calculations

Ethanol MW: 46 daltons
Specific gravity: 0.7939 (~0.8) g/mL
Volume of distribution (Vd): 0.6 L/kg

$$\text{Serum ethanol concentration (mg/dL)} = \frac{\text{dose (mg)}}{\text{Vd (L/kg)} \times \text{body weight (kg)} \times 10}$$

$$\text{mmol} = \frac{\text{mg}}{\text{MW}} = \frac{\text{mg}}{46\text{mg/mmoL}}$$

$$\text{mmol/L} = \frac{\text{mg/dL}}{4.6}$$

For a 70-kg individual:

Dose of ethanol	Predicted blood ethanol concentration
10 mL/kg of 10% (20 proof)	167 mg/dL (36.30 mmol/L)
3 mL/kg of 10% (20 proof)	50 mg/dL (10.87 mmol/L)
1.5 mL/kg of 10% (20 proof)	25 mg/dL (5.43 mmol/L)
150 mL (5 "shots") of 40% (80 proof)	143 mg/dL (31.09 mmol/L)
30 mL (1 "shot") of 40% (80 proof)	27 mg/dL (5.87 mmol/L)

Blood concentration consistent with legal intoxication = 10.87–17.39 mmol/L (50–80 mg/dL or 0.05–0.08 g/dL [%])

Average reduction in blood ethanol concentration (elimination phase):
Nontolerant adult: 3.26–4.35 mmol/L/h (15–20 mg/dL/h, 100–125 mg/kg/h)
Tolerant adult: 6.52–8.70 mmol/L/h (30–40 mg/dL/h, 175 mg/kg/h)

Case reports and retrospective case series suggest that chronic ethanol consumption may predispose a person to acetaminophen (APAP) hepatotoxicity (Chap. 34) even when APAP has been taken according to the manufacturer's recommended dosage of not more than 4 g daily. This has not been demonstrated in clinical trials.

Pathophysiology

Ethanol metabolism through the hepatic CYP2E1 pathway generates highly reactive oxygen radicals, including the hydroxyethyl radical (HER) molecule. Elevated oxygen radical concentrations generate a state of oxidative stress, which leads to cell damage. Oxygen radicals can also initiate lipid peroxidation resulting in reactive molecules such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE). These molecules react with proteins or acetaldehyde to form adducts that contribute to the development of alcoholic liver injury.

Oxidation of ethanol generates an excess of reducing potential in the cytosol in the form of NADH with the ratio of NADH to NAD^+ being dramatically increased. This ratio, also known as the redox potential, determines the ability of the cell to carry on various oxidative processes.

CLINICAL FEATURES

Ethanol is a selective central nervous system (CNS) depressant at low doses and a general depressant at high doses. Initially it depresses those areas of the brain involved with highly integrated functions. Cortical release leads to animated behavior and the loss of restraint. This paradoxical CNS stimulation is a result of disinhibition. In cases of mild intoxication, the signs of ethanol inebriation are quite

variable. The patient may be energized and loquacious, expansive, emotionally labile, and increasingly gregarious, or may appear to have lost self-control, exhibit antisocial behavior, and be ill tempered. As the degree of intoxication increases, there is successive inhibition and impairment of neuronal activity. The patient may become irritable, abusive, aggressive, violent, dysarthric, confused, disoriented, or lethargic. With severe intoxication, there is loss of airway protective reflexes, coma, and an increasing risk of death from respiratory depression. An ethanol-naive adult with a blood ethanol concentration of greater than 250 mg/dL (54.35 mmol/L) is usually comatose. The degree to which all of these effects manifest depends on the tolerance of the individual.

A patient may present with obvious signs and symptoms consistent with ethanol intoxication that include flushed facies, diaphoresis, tachycardia, hypotension, hypothermia, hypoventilation, mydriasis, nystagmus, vomiting, dysarthria, muscular incoordination, ataxia, altered consciousness, and coma. The presence or absence of an odor of ethanol on the breath is an unreliable means of ascertaining whether a person is intoxicated or whether ethanol was recently consumed. Diplopia, visual disturbances, and nystagmus may be evident, which may be caused by the toxic effects of ethanol or may represent Wernicke encephalopathy. Hypothermia may be exacerbated by environmental exposure, by malnutrition and loss of carbohydrate or energy substrate, and by ethanol-induced vasodilation. Acute altered mental status in an alcoholic patient can result from a variety of causes, including acute ethanol or toxic alcohol intoxication, hypoglycemia, therapeutic or illicit drug overdose, Wernicke-Korsakoff syndrome, head trauma, a postictal condition, infection, an intracranial hematoma (acute or chronic), hepatic encephalopathy, an electrolyte or acid–base disorder, or ethanol withdrawal.

DIAGNOSTIC TESTS

Immunoassay or gas chromatography is commonly used for determination of ethanol in liquid specimens in most hospitals. Hospital laboratory analysis of blood samples for ethanol content is usually based on serum. Breath testing and saliva testing are sometimes used in the clinical setting.

Blood tests that should be considered for patients with ethanol intoxication or alcoholic ketoacidosis include a complete blood count (CBC), electrolytes, BUN, creatinine, ketones, acetone, lipase, liver enzymes, prothrombin time (PT), ammonia, calcium, and magnesium. Patients with an anion gap metabolic acidosis should have urine ketones and a serum lactate concentration (Chaps. 17 and 103). High serum acetone concentrations may be indicative of isopropanol intoxication, whereas elevated serum or urinary ketones may be indicative of alcoholic ketoacidosis, starvation ketosis, or diabetic ketoacidosis. Because the laboratory nitroprusside reaction detects only ketones (acetoacetate and acetone) and not β-hydroxybutyrate, the assay for urinary ketones in patients with alcoholic ketoacidosis may be only mildly positive.

A blood ethanol concentration should be included in the initial laboratory studies. Comatose patients with concentrations below 300 mg/dL (65.22 mmol/L) and those with values in excess of 300 mg/dL (65.22 mmol/L) who fail to improve clinically during a limited period of close observation should have a head CT scan, followed by a lumbar puncture if warranted.

MANAGEMENT OF THE INTOXICATED PATIENT

Any patient presenting to the emergency department with an acute altered mental status mandates immediate investigation and treatment of reversible

etiologies such as hypoxia, hypoglycemia, and opioid intoxication. In addition, Wernicke encephalopathy should be considered. Abnormal vital signs should be addressed and stabilized. Patients who are combative and violent should be physically, and then chemically, restrained. The patient's fluid and electrolyte status should be assessed and abnormalities corrected.

No pharmacologic intervention has proven effective in reversing the intoxicating effects of ethanol or to enhance its elimination. Hemodialysis is an effective means of enhancing the systemic elimination of ethanol in patients with severe ethanol poisoning resulting in respiratory failure or coma, and may be an adjunctive treatment to supportive care. However, this is rarely indicated or necessary.

INDICATIONS FOR HOSPITALIZATION

A patient with uncomplicated ethanol intoxication can be safely discharged from the emergency department after a careful observation including consideration of social service or psychiatric counseling. An individual should not be discharged while still clinically intoxicated. However, consideration may be given to a situation where the intoxicated patient is discharged to a protected environment under the supervision of a responsible, non-intoxicated adult. In this case, the clinical assessment of the patient is more important than the blood ethanol concentration. Indications for hospital admission include persistently abnormal vital signs, persistently abnormal mental status with or without an obvious cause, a mixed overdose with other concerning xenobiotics, concomitant serious trauma, consequential ethanol withdrawal, and patients with an associated serious disease process such as pancreatitis or gastrointestinal hemorrhage.

ETHANOL-INDUCED HYPOGLYCEMIA

Hypoglycemia associated with ethanol consumption is believed to occur when ethanol metabolism provides a high cellular redox ratio. Hypoglycemia typically occurs when there is a reduced caloric intake and only after the hepatic glycogen stores are depleted, as in an overnight fast. Children have less glycogen stores than adults and are more likely to develop hypoglycemia.

Patients with ethanol-associated hypoglycemia usually present with an altered consciousness 2–10 hours following ethanol ingestion. Other physical findings include hypothermia and tachypnea. Laboratory findings, in addition to hypoglycemia, usually include a positive blood ethanol concentration, ketonuria without glucosuria, and mild acidosis. Management of ethanol-induced hypoglycemia is similar to other causes of hypoglycemia (Chap. 48).

ALCOHOLIC KETOACIDOSIS

The development of alcoholic ketoacidosis (AKA) requires a combination of physical and physiologic events to occur, each of which may be independent of the others. The normal response to starvation and depletion of hepatic glycogen stores is for amino acids to be converted to pyruvate. The high redox state favors the conversion of pyruvate to lactate, diverting pyruvate from being a substrate for gluconeogenesis. As an alternative source of energy, the body mobilizes fat from adipose tissue and increases fatty acid metabolism. This process results in the formation of acetoacetate. Most of the acetoacetate is then reduced to β-hydroxybutyrate as a consequence of the excess reducing potential or low redox state of the cell.

The diagnosis of AKA is a diagnosis of exclusion. Patients with AKA are typically chronic ethanol users, presenting after a few days of "binge" drinking and decreased oral intake. The patient may appear acutely ill with dehydration, tachypnea, tachycardia, and hypotension.

The blood ethanol concentration is usually low or undetectable because ethanol intake ceased substantially earlier in the clinical course. The hallmarks of AKA include an elevated anion gap metabolic acidosis with a serum lactate concentration insufficient to account for the gap. Ketones in serum and urine may be negative or mildly positive. The blood glucose may be low or mildly elevated.

Treatment should begin with adequate crystalloid fluid replacement, dextrose, and thiamine. Supplemental multivitamins, potassium, and magnesium should be instituted on an individual basis. Administration of either insulin or sodium bicarbonate in the management of AKA is usually unnecessary.

ALCOHOLISM

Alcoholism is traditionally defined as a chronic, progressive disease characterized by tolerance and physical dependence to ethanol, and pathologic organ changes. Alcoholism is a multifactorial, genetically influenced disorder and should be suspected in any patient who presents to the emergency department with unexplained trauma, seizures, or inappropriate behavior. Physical findings associated with long-term alcoholism include flushed facies, parotid enlargement, gynecomastia, cardiomyopathy, hepatomegaly, stigmata of cirrhosis, testicular atrophy, palmar erythema, Dupuytren contractures, peripheral neuropathy, nutritional deficiencies, and recurrent infections.

Concern for early detection and intervention led to attempts to create reliable diagnostic screening systems. The Brief Michigan Alcoholism Screening Test (MAST) and the CAGE (cut down, annoyance, guilt, eye-opener) questions represent two such tools. These tools emphasize the social and behavioral concomitants of heavy drinking. In the emergency department setting, questions concerning the patient's ability to function physically and psychologically are just as appropriate as quantifying the amount of ethanol consumed per day.

Although it is a serious disease with important health and economic consequences, alcoholism remains underdiagnosed and a treatment challenge. Various strategies are employed to treat alcoholism, including psychosocial interventions, pharmacologic interventions, or both. Naltrexone reduces the risk of relapse to heavy drinking and the frequency of drinking but does not substantially enhance abstinence. Acamprosate reduces drinking frequency, although its effects on enhancing abstinence are less clear. Disulfiram may reduce drinking frequency but may not support improved continuous abstinence rates. The data on serotonergic drugs is limited and not encouraging. The nonpharmacologic treatments for alcoholism may also be successful. Data derived from several studies and membership surveys indicate that short-term recovery rates of 40–80% can be achieved in treatment programs based on the 12-step approach of Alcoholics Anonymous.

Thiamine Hydrochloride

BIOCHEMISTRY

Thiamine (vitamin B_1) is a water-soluble vitamin that is essential in the creation and use of cellular energy. As a coenzyme in the pyruvate dehydrogenase complex, thiamine diphosphate, the active form of thiamine, accelerates the conversion of pyruvate to acetyl-coenzyme A (acetyl-CoA) (Fig. 13–1). This process links anaerobic glycolysis to the Krebs cycle, where subsequent aerobic metabolism produces the equivalent of 36 moles of adenosine triphosphate (ATP) from each mole of glucose. Thiamine is also required as a cofactor for α-ketoglutarate dehydrogenase, a second enzyme in the Krebs cycle, and for transketolase, an enzyme in the pentose phosphate pathway, in which nicotinamide adenine dinucleotide phosphate (NADPH) is formed for subsequent use in reductive biosynthesis.

Thiamine requirements are determined by total caloric intake and energy demand, with a minimum daily requirement of 0.5 mg/1000 calories. Thiamine is available from natural sources, such as organ meats, yeast, eggs, and green leafy vegetables. Thiamine is also synthesized as a hydrochloride salt.

PHARMACOLOGY

Thiamine is well absorbed from the human gastrointestinal tract. Chronic liver disease, folate deficiency, steatorrhea, and other forms of malabsorption all significantly decrease the absorption of thiamine. This malabsorption has even greater clinical relevance in alcoholics. Thiamine is eliminated from the body largely by renal clearance, which consists of a combination of glomerular filtration, flow-dependent tubular secretion, and saturable tubular reabsorption.

THIAMINE DEFICIENCY

Pathophysiology

Animals develop signs of encephalopathy 10 days after being rendered thiamine deficient. These animals demonstrate a breakdown of the blood–brain barrier with resultant extravasation of albumin and hemorrhage into the mammillary body, similar to findings described in humans with Wernicke encephalopathy.

Animal models offer insight into the mechanisms involved in developing thiamine-deficient neurologic injury. These models demonstrate an increase in concentrations of glutamate, followed by increases in lactate in vulnerable regions of the brain that can be blocked by the administration of the calcium channel blocker, nicardipine. This suggests a strong role for excitatory amino acid-induced alterations in calcium transport in the genesis of thiamine-deficient encephalopathy. In other animal models of thiamine deficiency, neuronal tissues are also directly injured by oxidative stress and lipid peroxidation.

Clinical Manifestations

When thiamine is completely removed from the human diet, clinical manifestations of thiamine deficiency typically develop within 2–3 weeks, although tachycardia, the first sign of deficiency, may occur as early as 9 days after ces-

sation of thiamine intake. The clinical symptoms of thiamine deficiency present as two distinct patterns: "wet" beriberi or cardiovascular disease, and "dry" beriberi, the neurologic disease known as Wernicke-Korsakoff syndrome. Although some patients display symptoms consistent with both disorders, usually either the cardiovascular or the neurologic manifestations predominate. A genetic variant of diminished transketolase activity, combined with low physical activity and a low-carbohydrate diet, may predispose to neurologic symptoms, whereas a high-carbohydrate diet and increased physical activity lead to cardiovascular symptoms.

Wet beriberi results from high-output cardiac failure induced by peripheral vasodilation and the formation of arteriovenous fistulae secondary to thiamine deficiency. Patients complain of fatigue, decreased exercise tolerance, shortness of breath, and peripheral edema. The classic triad of oculomotor abnormalities, ataxia, and global confusion defines Wernicke encephalopathy. Other manifestations include hypothermia and the absence of deep-tendon reflexes. Korsakoff psychosis, an irreversible disorder of learning and processing of new information characterized by a deficit in short-term memory and confabulation that often occurs together with Wernicke encephalopathy. A 10–20% mortality rate is associated with Wernicke encephalopathy, with survivors having an 80% risk of developing Korsakoff psychosis.

Populations at Risk

The alcoholic patient, whose consumption of ethanol is his or her major source of calories, is the best described and most easily recognized patient at risk for thiamine deficiency. Thiamine deficiency is also described in inmates; postoperative patients; in those patients with hyperemesis gravidarum or anorexia nervosa; in those patients receiving parenteral nutrition; in patients with acquired immunodeficiency syndrome (AIDS); in patients with malignancies; in the institutionalized elderly; patients with congestive heart failure on furosemide therapy; and in patients receiving hemodialysis.

INDICATIONS FOR THIAMINE REPLACEMENT

Thiamine hydrochloride is included in the initial therapy for any patient with an altered mental status, potentially acting as both treatment for and prevention of Wernicke encephalopathy. Because the morbidity and mortality associated with Wernicke encephalopathy are so severe, and treatment is both benign and inexpensive, thiamine hydrochloride should be included in the initial therapy for all patients who receive dextrose, for all patients with altered consciousness, and for every potential alcoholic or nutritionally deprived individual who presents to the emergency department or other clinical setting.

DOSING AND ADMINISTRATION

Initial therapy consists of the immediate parenteral administration of 100 mg of thiamine hydrochloride. This can be given either intramuscularly or intravenously, but the oral route should be avoided because of its unpredictable absorption. In some patients, symptoms such as ophthalmoplegia are reported to respond rapidly to as little as 2 mg of thiamine; however, the other neurologic and cardiovascular manifestations of thiamine deprivation may necessitate higher doses and may respond more slowly, if at all. Although virtually every source recommends that daily doses of 100 mg of thiamine are suffi-

cient as therapy, a recent trial suggested improved cognitive function when a daily dose of 200 mg was compared to lower doses. In fact, up to 1000 mg of thiamine hydrochloride can be used in the first 12 hours if a patient demonstrates persistent neurologic abnormalities.

A supplementary indication for the administration of thiamine hydrochloride occurs in patients with ethylene glycol poisoning. A minor pathway for the elimination of glyoxylic acid involves its conversion to α-hydroxy-β-ketoadipate by α-ketoglutarate:glyoxylate carboligase, a thiamine- and magnesium-dependent enzyme.

Routine thiamine administration should also be considered in patients with congestive heart failure and long-term use of diuretics. In one study, a daily dose of 200 mg of intravenous thiamine was able to increase cardiac ejection fraction by 22% at 7 weeks in patients using diuretics.

ADVERSE EVENTS

Very few complications are associated with the parenteral administration of thiamine. Although anaphylactic reactions occur, they are uncommon. The safety of thiamine use was evaluated in a large case series in which nearly 1000 patients received parenteral doses of up to 500 mg of thiamine without significant complications.

PREGNANCY CATEGORY

Thiamine hydrochloride is listed as pregnancy category A and is considered safe for use in lactating mothers.

AVAILABILITY

Multiple manufacturers formulate thiamine hydrochloride for intravenous or intramuscular administration. Typical concentrations are either 50 or 100 mg/mL.

76 Ethanol Withdrawal

Although it was widely recognized that alcoholics had a high incidence of delirium and psychomotor agitation, it remained controversial as to whether this was a result of ethanol use, ethanol abstinence, or coexisting psychological disorders until the 1950s. Currently, alcoholism and alcohol withdrawal syndromes represent a major problem in both the inpatient and outpatient settings.

CLINICAL SYNDROMES

Alcohol withdrawal is defined in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) as the cessation of heavy or prolonged alcohol use resulting within a period of a few hours to several days in the development of 2 or more of the clinical findings listed in Table 76–1. Furthermore, these symptoms must have no other organic etiology. Although alcohol withdrawal syndromes can be classified both by timing (early vs. late) and by severity (complicated vs. uncomplicated), there are no adequate or fully accepted criteria by which to define these categories. Additionally, the clinical course of alcohol withdrawal syndrome (AWS) can vary widely among patients and progression of individual patients through these different stages is extremely variable. In fact, some heavy alcohol users experience no withdrawal syndrome following the cessation of alcohol consumption. Because of the subjective nature of many of these findings, we discourage the use of pure clinical descriptors (such as delirium tremens) to classify the severity of alcohol withdrawal in any given patient.

Early Uncomplicated Withdrawal

Alcohol withdrawal begins as early as 6 hours after the cessation of drinking. Early withdrawal is characterized by autonomic hyperactivity including tachycardia, tremor, hypertension, and psychomotor agitation. Although these symptoms are uncomfortable, they are not generally dangerous. Of the patients who ultimately develop severe manifestations of AWS, most initially develop these findings, but not invariably. At this stage of AWS, the symptoms are still readily amenable to treatment with ethanol, as is done daily by most heavy alcohol users.

Alcoholic Hallucinosis

Nearly 25% of patients with AWS develop hallucinations, and a subset of these patients develop alcoholic hallucinosis, a syndrome of persistent, typically tactile or visual, hallucinations. However, as opposed to what is observed with delirium tremens (DTs), alcoholic hallucinosis is associated with a clear sensorium.

Alcohol Withdrawal Seizure

Approximately 10% of patients with AWS develop alcohol withdrawal seizures, or "rum fits." For many patients, a generalized alcohol withdrawal seizure may be the first manifestation of the AWS. Approximately 40% of patients with alcohol withdrawal seizures have an isolated seizure, and 3% develop sta-

TABLE 76–1. DSM-IV Criteria for Alcohol Withdrawal

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after criterion A:
   1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100)
   2. Increased hand tremor
   3. Insomnia
   4. Nausea or vomiting
   5. Transient visual, tactile, or auditory hallucinations or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Grand mal seizures
C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a general condition and are not better accounted for by another mental disorder.

tus epilepticus. Alcohol withdrawal seizures may occur in the absence of other signs of alcohol withdrawal and are characteristically brief, generalized tonic-clonic events with a short postictal period. Rapid recovery and normal mental status belie the seriousness of an alcohol withdrawal seizure. However, for approximately one-third of patients with DTs, the sentinel event is an isolated alcohol withdrawal seizure.

Delirium Tremens

Delirium tremens is the most serious complication of the AWS, and it generally manifests between 48 and 96 hours after the cessation of drinking. Many of the clinical manifestations of DTs are similar to those of uncomplicated early alcohol withdrawal, differing only in severity. These clinical manifestations include tremor, autonomic instability (hypertension and tachycardia), and psychomotor agitation. However, unlike AWS, DTs, as defined in DSM-IV, is associated with either (a) disturbance of consciousness (such as reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention, delirium, confusion, and frank psychosis, or (b) a change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia. Unlike the early manifestations of alcohol withdrawal, which after the cessation of drinking typically last for 3–5 days, DTs can last for as long as 2 weeks.

PATHOPHYSIOLOGY

The effects of chronic alcohol consumption on neurotransmitter function best explain the clinical findings. Persistent stimulation of the inhibitory γ-aminobutyric acid (GABA) receptor-chloride channel complex by ethanol, leads to downregulation of the GABA receptor-chloride channel complex. This allows the alcohol user to maintain a relatively normal level of consciousness despite the presence of sedative concentrations of ethanol in the brain. A continued escalation of the steady state ethanol concentration is required to achieve euphoria (ie, tolerance) which results in progressive desensitization of the GABA receptor-chloride channel complex. A converse series of events

occurs at the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor. Withdrawal of alcohol is associated with both a decrease in GABAergic activity and an increase glutamatergic activity. This phenomenon of a concomitant increased excitation and loss of inhibition results in the clinical manifestations of autonomic excitability and psychomotor agitation.

PREDICTORS FOR THE DEVELOPMENT OF ALCOHOL WITHDRAWAL

The strongest predictor for the development of AWS is a history of prior episodes of AWS/DTs and/or a family history. One of the more commonly used means for accurately assessing alcohol withdrawal is the Clinical Institute Withdrawal Assessment (CIWA-Ar) score.

Clinical and Biochemical Predictors

Numerous attempts have been made to develop biochemical predictors for the presence and/or severity of alcohol withdrawal. The presence of an elevated admission ethanol concentration for a patient already in withdrawal is a predictor for more severe alcohol withdrawal.

MANAGEMENT

Alcohol Withdrawal Seizures

Although alcohol withdrawal seizures are generally self-limited, benzodiazepines are the preferred agent for patients with persistent or recurrent alcohol withdrawal seizures. There is no role for phenytoin in either treatment or prevention of alcohol withdrawal seizures. The most likely explanation for the failure of phenytoin is its inability to regulate GABA or NMDA receptors, the principle mediators of seizures in alcohol withdrawal. One exception to this lack of usefulness occurs in the alcoholic patient with a nonalcohol withdrawal seizure or a history of underlying seizure disorders.

Alcohol Withdrawal

In the early stages of alcohol withdrawal, many patients are able to self-medicate with additional ethanol consumption. Among those who seek medical attention, many patients with AWS can be safely managed as outpatients. Those individuals not candidates for outpatient management should be referred to inpatient detoxification centers or medical units, depending on the severity of withdrawal and other comorbid conditions.

Initial management should include a thorough assessment to identify any coexisting medical, psychiatric, or toxicologic disorders. In particular, an assessment for central nervous system trauma and infection should include the liberal use of computed tomography and lumbar puncture. Patients with altered cognition and an elevated body temperature should receive antibiotics pending the performance and results of the lumbar puncture. Thiamine should be given to all patients to prevent the development of Wernicke encephalopathy.

Oral benzodiazepine administration is generally effective in patients with early or mild AWS, although initial rapid titration with an intravenous regimen may be more efficient. Intravenous diazepam offers the most rapid time to peak clinical effects which limits oversedation. Lorazepam has a delayed

peak clinical effect of approximately 10–20 minutes, which may lead to redosing before the prior dose has achieved peak effect. Midazolam may be administered intramuscularly if intravenous access is not available, but is slowly absorbed by this route. Although no significant differences are observed between benzodiazepines and barbiturates in terms of mortality or the duration of delirium, the improved pharmacokinetic profile and ease of administration favor benzodiazepines as the preferred initial medication.

The initial management of patients with AWS/DTs should include rapid titration with intravenous benzodiazepines to achieve sedation. The goal of therapy is to have the patient sedated but breathing spontaneously with normal vital signs. In many patients, complete sedation may allow for autotitration; that is, as the AWS resolves the blood concentrations of diazepam and desmethyldiazepam fall, allowing gradual recovery. Multiple studies now suggest that if additional doses are required, they should be administered based on symptoms ("symptom triggered") as opposed to a fixed dosing schedule. However, it is important to note, that the decision to treat in the symptom-triggered group was made based on CIWA score (usually >8), emphasizing the usefulness of standardized scoring and evaluation tools.

Resistant Alcohol Withdrawal and Delirium Tremens

There is a subgroup of patients with AWS who require very large doses of diazepam or another comparable medication to achieve initial sedation. This same group often has exceedingly high benzodiazepine requirements to maintain this level of sedation. Subjects with resistant AWS and DTs may have massive benzodiazepine requirements exceeding 2600 mg of diazepam in the first 24 hours and generally require admission to an intensive care or stepdown unit.

The approach to the management of resistant AWS depends on several factors including the availability of an intensive care unit bed. In the ICU, despite the perception of failure of high benzodiazepine requirements, we favor continued administration of benzodiazepines in a symptom triggered fashion. Patients who receive this therapy generally respond to bolus doses of diazepam ranging from 10–100 mg, which results in a brief period of sedation followed by recrudescence of their AWS. In non-ICU settings, the ability to administer frequent intravenous doses of diazepam is limited, and the use of intravenous infusions of secondary sedative medications may be more practical.

Phenobarbital, given in combination with a benzodiazepine, in intravenous doses of 130 mg is a reasonable choice. Caution is required to avoid stacking doses of phenobarbital as the onset of clinical effect takes approximately 20–40 minutes. Alternatively, propofol in standard doses may be administered, and although rapid in onset, is somewhat difficult to titrate.

Ethanol

Little controlled data exist on the role of ethanol, whether orally or by infusion, for the in-hospital treatment of AWS/DTs. The potential for significant complications and difficulty in safely administering this therapy makes it inappropriate to recommend this regimen.

Adrenergic Antagonists

Both β-adrenergic antagonists and clonidine reduce blood pressure and heart rate in randomized placebo-controlled trials. However, the inability of these

medications to address the underlying pathophysiologic mechanism of AWS and subsequently control the neurologic manifestations makes them suboptimal as sole therapeutic interventions.

Magnesium

Aside from repletion of electrolyte abnormalities, there is no indication for routine administration of magnesium for the treatment of AWS.

77 Disulfiram and Disulfiramlike Reactions

Disulfiram, tetraethylthiuram disulfide, and related chemicals are used as catalytic accelerators for the vulcanization (stabilization) of rubber by the addition of sulfur. In the early 1900s, workers exposed to disulfiram developed adverse reactions when exposed to ethanol. This finding gave rise to the use of disulfiram as an adjunct in the treatment of alcoholism. Although the evidence to support the use of disulfiram therapy as part of a comprehensive alcohol treatment program is equivocal, it is still used commonly today. Disulfiram toxicity results from disulfiram–ethanol reactions, acute overdose, and chronic therapy.

PHARMACOKINETICS AND TOXICOKINETICS

Disulfiram is highly lipid soluble and very insoluble in water. Following ingestion, disulfiram is either absorbed as the parent compound or converted to diethyldithiocarbamic acid (diethyldithiocarbamate) in the acid environment of the stomach. Diethyldithiocarbamic acid is very unstable in stomach acid and rapidly undergoes absorption, spontaneous decomposition to carbon disulfide and diethylamine, or chelates copper, forming a bis(diethyldithiocarbamate)–copper complex. Approximately 70–90% of an ingested therapeutic dose of disulfiram is absorbed as this bis(diethyldithiocarbamate)–copper complex, with peak serum concentrations achieved 8–10 hours following a 250-mg dose. Both the parent compound and the metabolites are highly protein bound.

Following a 250-mg dose, the half-lives of disulfiram, diethyldithiocarbamate, and carbon disulfide are 7.3 ± 1.5 hours, 15.5 ± 4.5 hours, and 8.9 ± 1.4 hours, respectively.

DISULFIRAM–ETHANOL REACTION

Pathophysiology

Ethanol is metabolized by alcohol dehydrogenase to acetaldehyde, which normally is rapidly converted to acetate by aldehyde dehydrogenase. Disulfiram and its metabolites inhibit aldehyde dehydrogenase leading to 5–10-fold rise in acetaldehyde concentrations above baseline. The exact mechanism for the effect of disulfiram is unclear, but may involve inactivation of aldehyde dehydrogenase by causing internal sulfur–sulfur bonds, or by competing for nicotinamide adenine dinucleotide. Chemicals structurally similar to disulfiram including carbon disulfide, tetramethylthiuram disulfide (thiram), and tetramethylthiuram monosulfide are also recognized to cause reactions with ethanol. Many xenobiotics produce similar symptoms following ethanol exposure (Table 77–1).

The duration of disulfiram's inhibition of aldehyde dehydrogenase is partially dependent on the dose ingested. A 500-mg dose inhibits aldehyde dehydrogenase for up to 4 days, a 1000-mg dose for up to 6 days, and a 1500-mg dose for up to 8 days.

Accumulation of acetaldehyde is responsible for the symptoms produced by the disulfiram–ethanol reaction. In fact, intravenous administration of

TABLE 77–1. Xenobiotics Reported to Cause a Disulfiramlike Reaction with Ethanol

Antimicrobials
Cephalosporins, especially those that contain a methylthiotetrazole (MTT) side chain, such as cefotetan, cefoperazone, cefamandole, and cefmenoxime.
Metronidazole
Moxalactam
Trimethoprim-sulfamethoxazole
Possible reactions with chloramphenicol, griseofulvin, quinacrine, procarbazine, phentolamine, nitrofurantoin
Sulfonylurea oral hypoglycemics
Chlorpropamide
Tolbutamide
Chemicals
Calcium carbimide (citrated)
Carbon disulfide
Carbon tetrachloride
Chloral hydrate
Dimethylformamide
Nitrefazole
Tetraethylthiuram disulfide (disulfiram)
Tetramethylthiuram disulfide (thiram)
Thiram analogs (fungicides)
Copper, mercuric, and sodium diethyldithiocarbamate
Zinc and ferric dimethyldithiocarbamate
Zinc and disodium ethylenebis (dithiocarbamate)
Trichloroethylene
Mushrooms
Coprinus mushrooms including *C. atramentarius*, *C. insignis*, *C. variegatus*, and *C. quadrifidus*, *Boletus luridus*, *Clitocybe clavipes*, *Polyporus sulphureus*, *Pholiota squarosa*, *Tricholoma aurantum*, and *Verpa bohemica*

acetaldehyde to humans produces similar symptoms as to those experienced by patients taking disulfiram who consume ethanol. Acetaldehyde secondarily increases the release of histamine, which may also contribute to toxicity.

Clinical Effects

Most patients taking disulfiram who are exposed to ethanol develop symptoms of the disulfiram-ethanol reaction within 15 minutes. The symptoms usually peak within 60 minutes, and then gradually subside over the next few hours, but may persist as long as ethanol is available to be metabolized to acetaldehyde. Signs and symptoms include facial and generalized body warmth and flushing, conjunctival injection, pruritus, urticaria, diaphoresis, lightheadedness, vertigo, headache, nausea, vomiting, and abdominal pain. Cardiac effects include palpitations, chest pain, and dyspnea. Tachycardia and hypotension are common and orthostatic hypotension can lead to syncope. ECG abnormalities consistent with myocardial ischemia are uncommon and usually occur in the setting of severe hypotension. Rare complications include shock, hypertension, bronchospasm, and methemoglobinemia. Esophageal rupture and intracranial hemorrhage may occur secondary to vomiting.

Diagnostic Testing

Disulfiram blood concentrations are not useful when managing most patients with suspected disulfiram toxicity following an acute overdose, chronic therapy, or a disulfiram–ethanol reaction. In most patients with suspected disulfiram–ethanol reactions it is important to confirm the presence of ethanol, as this will provide information about the expected duration of symptoms. Because only small amounts of ethanol can precipitate a disulfiram–ethanol reaction, some patients, especially those with small ingestions or dermal exposures, may not have clinically detectable ethanol concentrations at the time of evaluation.

Management

Symptomatic and supportive care are the mainstays of treatment. Gastrointestinal decontamination is unnecessary as ethanol is rapidly absorbed and most patients will have substantial vomiting. Antiemetics may improve nausea and vomiting, and histamine (H_1) receptor antagonists, such as diphenhydramine, may improve cutaneous flushing. Parenteral administration of these medications is preferred to assure absorption. Intravenous crystalloid administration is required for hypovolemia. If hypotension is refractory to crystalloid administration a vasopressor should be administered. There is a theoretical benefit to administering a direct-acting vasopressor such as norepinephrine, because disulfiram inhibits dopamine β-hydroxylase, an enzyme necessary for norepinephrine synthesis.

Because fomepizole inhibits alcohol dehydrogenase, it can prevent the production of acetaldehyde. A patient on disulfiram experiencing a disulfiram–ethanol reaction was given fomepizole experimentally with an almost immediate decrease in the serum acetaldehyde concentration and a rapid clinical improvement. Likewise, hemodialysis can remove ethanol. However, fomepizole and hemodialysis should only be considered for patients with life-threatening signs or symptoms refractory to standard treatment.

ACUTE DISULFIRAM OVERDOSE

Clinical Manifestations

Acute overdose of disulfiram is uncommon and typically does not cause life-threatening toxicity. Most patients will develop symptoms within the first 12 hours following ingestion, which resolve by 24 hours after ingestion. Nausea, vomiting, and abdominal pain are common. A spectrum of central nervous system depression from drowsiness to coma may occur. Metabolic acidosis is rare. Dysarthria and movement disorders, including myoclonus, ataxia, dystonia, and akinesia, occur rarely. These movement disorders may be related to direct effects of carbon disulfide on the basal ganglia. Sensorimotor neuropathy, subacute weakness, and psychosis are uncommon. Hypotonia may be a prominent feature in children. Persistent neurologic abnormalities lasting for weeks to months are rare, but are reported in both children and adults.

Management

Unless contraindicated, activated charcoal, 1 g/kg of body weight, should be administered. It is unusual for a patient with an isolated disulfiram ingestion to require either orogastric lavage or whole-bowel irrigation. Syrup of ipecac is not indicated, especially because some formulations contain ethanol, which

could precipitate a disulfiram–ethanol reaction. General supportive measures should be instituted.

CHRONIC DISULFIRAM THERAPY

Most of the known adverse effects are derived from case reports. Toxicity from chronic disulfiram therapy correlates poorly with dose, and there is a wide variability in latency period between initiation of therapeutic dosing and the development of symptoms. Adverse effects most commonly involve the liver, the skin, or the central nervous system. Common effects include nausea, drowsiness, dizziness, headache, a metallic taste in the mouth, halitosis, and skin odor described as having a sulfur or garlic smell, decreased libido, impotence, and hypertension.

Disulfiram therapy also causes a spectrum of hepatotoxicity, ranging from asymptomatic minor elevations of the aminotransferases to fulminant hepatic failure and death. The mechanism of disulfiram-induced hepatotoxicity is poorly understood and may be idiosyncratic. The onset of hepatotoxicity usually varies from 2 weeks to 6 months after initiation of disulfiram therapy. Dermatoses associated with disulfiram therapy include exfoliative dermatitis, contact dermatitis, urticaria, pruritus, acne, and yellow palms. Some reported neuropsychiatric side effects include headache, dizziness, confusion, memory impairment, ataxia, parkinsonian symptoms, seizures, optic neuropathy, coma, peripheral neuropathy, psychosis, depression, catatonia, and organic brain syndrome.

Management

Once toxicity occurs, the drug must be discontinued. Monitoring serum aminotransferase concentrations, both before the initiation of therapy to establish a baseline and during the course of therapy, is recommended. Common recommendations for asymptomatic patients include monitoring aminotransferase at 2 weeks following initiation of disulfiram therapy and at 3–6-month intervals thereafter.

78 | γ-Hydroxybutyric Acid

Since its scientific discovery as a γ-aminobutyric acid (GABA) mimetic neurochemical, γ-hydroxybutyric acid (GHB) has been transformed from a drug of investigational importance and licit medical uses to the toxic ingredient in banned nutritional supplements and illicit recreational drugs. GHB and its numerous chemical precursors and structural analogs, most notably γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), represent a group of drugs among the broad class of recreational drugs known as "club drugs." Like most other "club drugs," GHB, GBL, and 1,4-BD are physically and psychologically addictive with acute and chronic toxicity that may be severe or lethal.

HISTORY AND EPIDEMIOLOGY

GHB was discovered in 1960 when it was synthesized as a structural analog of the inhibitory neurotransmitter GABA, which was capable of traversing the blood–brain barrier (BBB) after peripheral administration. Three years later, GHB was determined to be a naturally occurring neurochemical in the mammalian brain. GHB found its first clinical application as an anesthetic agent in the early 1960s. In 1966, the first associations of the effects of 1,4-BD with GHB were made. Although GHB continues to be investigated and used as an anesthetic adjuvant abroad, it has never gained widespread acceptance in the United States for this clinical application.

GHB later became popular as a sports supplement and "natural" soporific. In the late 1980s, GHB was introduced to the health and dietary supplement market with dubious claims that it could metabolize fat, enhance muscle building, and improve sleep. However, it was quickly associated with severe adverse effects and deaths. Accordingly, the US Food and Drug Administration (FDA) intervened in November 1990 to prohibit further nonprescription sale of GHB in nutritional supplements. This FDA ban was circumvented by substitution of GBL for GHB as the active ingredient in dietary supplements. Soon after its substitution into dietary health supplements, toxic effects similar to GHB, including deaths, were attributable to GBL. Consequently, the FDA issued a voluntary recall of GBL-containing health supplements in 1999. As was the case with the initial recall of GHB, GBL was substituted by yet another GHB precursor, 1,4-BD. Predictably, the consequences of 1,4-BD misuse and abuse were clinically similar to that of GHB and GBL, including death. GHB recently received both orphan drug and investigational new drug (IND) status from the FDA as a therapeutic agent for narcolepsy.

Illicit use of GHB and its analogs have primarily occurred in the (a) recreational setting of raves or night clubs; (b) athletic setting of bodybuilding gyms and fitness centers; (c) home consumer setting of individuals seeking its "natural health benefits"; and (d) criminal setting of drug-facilitated sexual assault. Whereas the illicit use of GHB and its precursors appear to have reached a plateau in the United States, recent statistics show GHB abuse to be on the rise internationally. For example, in Spain, GHB was responsible for 3.1% of all toxicologic emergencies in an urban public hospital emergency department during a 15-month study period, and ranked second in illicit

drugs requiring emergency consultation. Although European and Asian countries report rises in acute poisonings from GHB and its chemical precursors and structural analogs, virtually all of the reports of GHB dependence and withdrawal are from the United States.

PHARMACOLOGY

GHB has a dual pharmacologic profile, with the intrinsic neuropharmacology of endogenous GHB being distinct and divergent from that of exogenously administered GHB. The principal difference between their profiles is that the intrinsic neuropharmacologic activity of endogenous GHB appears to be mediated by the GHB receptor, whereas the neuropharmacologic activity of exogenously administered GHB is likely mediated by the $GABA_B$ receptor.

Endogenous GHB

Although GHB is heterogeneously distributed throughout the mammalian CNS, its highest concentrations are found in the hippocampus, basal ganglia, hypothalamus, striatum, and substantia nigra. The subcellular presynaptic synthesis of endogenous GHB involves 3 precursors (GABA, GBL, and 1,4-BD) and 5 enzymes (GABA-transaminase, succinic semialdehyde reductase [SSA reductase], alcohol dehydrogenase [ADH], aldehyde dehydrogenase [ALDH], and serum and peripheral tissue lactonases) (Fig. 78–1).

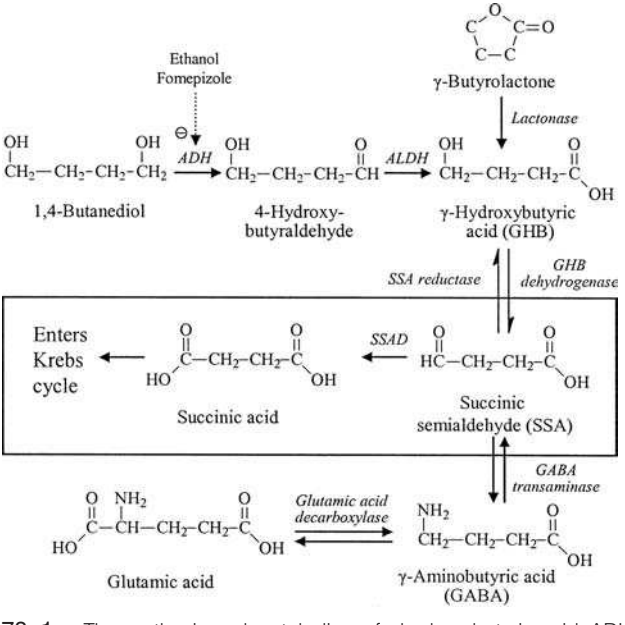

FIG. 78–1. The synthesis and metabolism of γ-hydroxybutyric acid. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; SSA reductase, succinic semialdehyde reductase; SSAD, succinic semialdehyde dehydrogenase.

The GHB receptor exhibits no binding affinity for GABA, baclofen, or glutamate, which have no capacity to displace radioactive GHB from this binding site. Activation of this receptor alters second messenger systems in the hippocampus by increasing cyclic guanosine monophosphate (cGMP) turnover and stimulating inositol phosphate turnover, which subsequently modulate the activity of other neurotransmitter systems. Low-dose GHB inhibits GABA release in the thalamus, which may implicate a role for GHB in producing absence seizures, and decreases the extracellular GABA concentration in the frontal cortex. However, higher doses of GHB enhance GABA concentrations in the frontal cortex. GHB also exerts a prominent modulatory effect on dopamine neurotransmission. Acute administration of GHB inhibits dopamine release and results in the accumulation of dopamine in the presynaptic cells. This attenuation of dopamine neurotransmission may be the pharmacologic basis for the loss of locomotor activity in experimental animals and overdose patients.

Despite having no binding affinity for opioid receptors, GHB increases the release of endogenous opioids throughout brain. As such, despite a lack of affinity for the GHB receptor, the administration of naloxone and naltrexone can attenuate or reverse the electrophysiologic and behavioral actions of GHB on dopamine neuron firing and catalepsy in experimental animals.

After its release from GHBergic presynaptic membranes, GHB activity is terminated by an active vesicular uptake system driven by the vesicular inhibitory amino acid transporter (the same transporter that mediates the vesicular uptake of GABA and glycine) or by an active cellular uptake from the synaptic cleft. Once within the cell, the degradation of endogenous GHB in the mammalian brain can occur via 4 pathways leading to succinic acid (which enters the tricarboxylic acid cycle), GABA, *trans*-4-hydroxycrotonic acid, or 4,5-dihydroxyhexanoic acid.

Exogenous GHB

The $GABA_B$ receptor mediates the pharmacologic, behavioral, clinical, and toxicologic actions of exogenous GHB and its precursors. When the brain GHB concentration exceeds its physiologic concentration by 2–3 orders of magnitude, it saturates GHB-specific receptors and produces $GABA_B$ receptor-mediated brain perturbations.

GHB and Endogenous Analogs

GHB has several *endogenous* structural analogs (GABA, *trans*-4-hydroxycrotonic acid) and chemical precursors (GBL, 1,4-BD, γ-crotonolactone [GCL]), as well as several *synthetic* structural analogs (5-hydroxyvaleric acid, γ-methyl-GHB, γ-phenyl-GHB, γ-(*p*-chlorophenyl)-GHB, γ-(*p*-methoxyphenyl)-GHB, γ-benzyl-GHB, *R*-γ-benzyl-GHB, *S*-γ-benzyl-GHB, γ-(*p*-methoxybenzyl)-GHB [NCS 435]) and precursors γ-valerolactone (GVL) and tetrahydrofuran (THF). Of these analogs, illicit abuse has only been reported with GBL, 1,4-BD, γ-methyl-GHB, GVL, and THF.

GBL, the lactone ring precursor analog of GHB, is an endogenous substance in the mammalian brain at present concentrations of approximately 10% that of GHB. Chemically, it is most commonly referred to as γ-butyrolactone, but it also has numerous obscure chemical synonyms that are often intentionally listed on illicit GBL product labels to conceal the identity of GBL, such as butyrolactone; 4-butyrolactone; 4-butanolide; tetrahydro-2-furanone;

4-deoxytetronic acid; butyrolactone-γ; 4-hydroxbutyric acid lactone; γ-hydroxybutyric acid lactone; butyryl lactone; butyric acid lactone; hydroxybutanoic acid lactone; tetrahydro-2-furanone; 1,4-butanolide; and 1,4-lactone. Based on the behavioral and analytical observations, GBL is best described as a precursor to the pharmacologically active metabolite GHB. 1,4-BD, the other naturally occurring GHB precursor analog, is usually referred to by the chemical name 1,4-butanediol, but it, too, has several additional chemical synonyms, including 1,4-butylene glycol; 1,4-dihydroxybutane; and 1,4-tetramethylene glycol. CNS depression by 1,4-BD is mediated through metabolism to GHB.

Synthetic Analogs

Numerous pharmacologically active synthetic GHB structural analogs have been produced in the laboratory. Although the list of pharmacologically active GHB structural analogs appears to be ever increasing, only GHV (γ-methyl-GHB) abuse is reported to date.

Synthetic Precursor Analogs

GVL and THF have been illicitly used as synthetic precursor analogs of GHV and GBL/GHB, respectively. GVL is the structural analog of GBL produced by the methylation of GBL in the γ (4-carbon) position. It has the chemical synonyms 4-hydroxypentanoic acid lactone, and γ-methyl-GHB. When administered, GVL undergoes hydrolysis to yield the GHB structural analog GHV. GVL is reported to be used in the illicit synthesis of GHV. THF is the cyclic ether structural analog of GBL. THF can serve as the key precursor ingredient in the illicit synthesis of GBL. Because THF is a widely employed industrial solvent, human toxicity generally occurs in the context of occupational exposure and poisoning, where THF causes nausea, headache, blurred vision, dizziness, narcosis, tinnitus, chest pain, and coughing.

PHARMACOKINETICS AND TOXICOKINETICS

GHB is rapidly and nearly completely absorbed from the gastrointestinal tract with an onset of action of about 15 minutes and a peak effect by 90–120 minutes. The steady-state volume of distribution is approximately 0.58 L/kg. GHB is eliminated very rapidly, with a half-life of 30 minutes. Less than 5% of the parent compound is recovered in the urine. In comparison, GBL is more rapidly absorbed and has a longer duration of action, which results from higher lipid solubility. Because 1,4-BD is metabolized by ADH, coingestion of ethanol or fomepizole can prolong its clinical effects because of competitive inhibition of ADH.

CLINICAL MANIFESTATIONS

In volunteers undergoing sleep studies, a clear oral dose–response effect for GHB was noted: 30 mg/kg produces CNS depression and myoclonus; 50 mg/kg produces unconsciousness; and 60 mg/kg produces coma. These clinical manifestations of overdose are highlighted by a number of well-documented cases. Although the constellation of signs and symptoms are best reported for GHB, the following is most likely applicable to the entire class of xenobiotics. Vital signs typically reveal hypotension, bradycardia, bradypnea, and hypothermia. Bradypnea is the most consequential of these effects, and apnea is

the most likely cause of death. Pupils are typically miotic and poorly responsive to light. Salivation and vomiting are common, especially when CNS depression is prominent. These effects compound bradypnea and hypoventilation in that they increase the risk for aspiration.

Central nervous system effects can range from hallucinations, disorientation, and agitation to lethargy followed by stupor and coma. These findings most likely represent disinhibition of higher cortical areas and are consistent with other sedative-hypnotics. In contrast to ethanol and other sedative-hypnotics, however, patients with GHB overdose often manifest aggression and violence following arousal or during an attempt to assess their gag reflex or perform intubation.

Motor abnormalities are also common, and there is debate about whether they represent seizures, myoclonus or both. In animal models, GHB can produce seizures, yet EEG monitoring in humans suggests that repetitive movements most likely represent myoclonus.

Other findings include prominent U waves on the ECG. Laboratory evaluation is usually normal.

The duration of effect is characteristically short. Many patients will abruptly awaken within a few hours of presentation, and appear completely normal. Even those patients who require endotracheal intubation are usually extubated within 8 hours. As long as aspiration and hypoxia have not occurred, most patients suffer no sequelae.

DIAGNOSTIC TESTING

The presence of GHB and related xenobiotics can be determined quantitatively and qualitatively, in both serum and urine, using a variety of analytical techniques. The most important caveat is that appropriate cutoff values must be selected to distinguish use and overdose from endogenous concentrations. In general, unconsciousness occurs when serum concentrations reach 50 μg/mL, and concentrations above 260 μg/mL typically produce deep coma. Attempts to relate concentrations to clinical effects in any individual might not be valid because of the potential for tolerance. Because most clinical hospital laboratories do not routinely test for the presence of GHB analogs, and recovery is typically rapid, results of analytical testing are not useful for clinical care.

TREATMENT

The provision of good supportive care remains the mainstay of therapy. The decision to perform endotracheal intubation should be made at the bedside and be based on a clinical assessment of oxygenation and ventilation. Despite deep coma, many patients will have adequate respirations and airway protective reflexes. As the duration of unconsciousness is relatively brief, coma in and of itself should not be considered an absolute indication for endotracheal intubation. Hypotension usually responds to fluids, and bradycardia rarely requires pharmacologic intervention. Hypothermia is mild and typically responds to passive external rewarming.

Dextrose and thiamine should be given as clinically indicated. Although no clinically available GHB antagonists exist, both naloxone and physostigmine have been used. A trial of naloxone is often clinically reasonable in the undifferentiated patient based on the findings of small pupils, CNS and respiratory depression. However, naloxone administration to GHB-toxic humans is usu-

ally unsuccessful. Although anecdotal reports suggest some usefulness for physostigmine, convincing data are lacking.

There is no role for any form of gastrointestinal decontamination. GHB and related analogs are rapidly absorbed and can produce significant airway compromise. It is unlikely that a significant percentage of the ingested dose will be present in the stomach at the time of presentation, and the use of activated charcoal will only increase the risk of vomiting and aspiration. However, if a coingestant is suspected appropriate decontamination techniques can be used as long as there are no contraindications.

GHB WITHDRAWAL

Severe and life-threatening manifestations follow abrupt cessation or reduction in intake of GHB or any of its precursors or analogs. The signs and symptoms are clinically consistent with sedative hypnotic withdrawal. Patients develop agitation, disorientation, hallucinations, hypertension, tachycardia, hyperthermia, tremor, and seizures, often within hours of their last use.

Treatment principles involve sedation, cooling, volume resuscitation, and a search for other medical and traumatic causes of alterations in behavior. Although benzodiazepines appear to be the safest initial pharmacologic agents to control behavior, excessively large doses may be required. When patients are resistant to benzodiazepines, either barbiturates or propofol can be given.

79 Inhalants

HISTORY AND EPIDEMIOLOGY

Inhalant abuse is defined as the deliberate inhalation of vapors for the purpose of changing one's consciousness or becoming "high." It is also referred to as volatile substance abuse and was first described in 1951. Inhalants are appealing to adolescents because they are inexpensive and readily and legally available.

The demographics of inhalant abuse differ markedly from those of other traditional substances of abuse. Estimates in the United States suggest that more than 2 million youths 12–17 years of age used inhalants at least once in their lifetime. Between 1994 and 2000 the number of new inhalant users increased more than 50%, and the median age of first use was 13 years. In the United States, the problem is greatest among children of lower socioeconomic groups; non-Hispanic white adolescents are the most likely to use inhalants.

Inhalant abuse includes the practices of sniffing, huffing, and bagging. Sniffing entails the inhalation of a volatile substance directly from a container, as occurs with airplane glue or rubber cement. Huffing, the most common method, involves pouring a volatile liquid onto fabric, such as a rag or sock, and placing it over the mouth and/or nose while inhaling. Bagging refers to placing a solvent into a plastic or paper bag and rebreathing from the bag several times; spray paint is among the agents commonly used with this method.

XENOBIOTICS USED

Most of the xenobiotics involved are commercially available volatile hydrocarbons that are mixtures of aliphatic and aromatic hydrocarbons. For example, gasoline is a mixture of more than 1500 compounds. Substituted hydrocarbons contain halogens or other functional groups (eg, hydroxyl or nitrite). The most commonly inhaled volatile hydrocarbons are fuels, such as gasoline, and solvents, such as toluene. Other commonly inhaled hydrocarbon-containing products include spray paints, lighter fluid, air fresheners, and glue. Although volatile alkyl nitrites are technically substituted hydrocarbons, they have pharmacologic and behavioral effects, as well as patterns of abuse that are distinct from the other volatile hydrocarbons. Amyl nitrite, the prototypical volatile alkyl nitrite, became popular in the 1960s with the appearance of "poppers," small glass capsules containing the chemical in a plastic sheath or gauze. The most commonly used nonhydrocarbon inhalant is nitrous oxide. Nitrous oxide is the propellant in supermarket-bought whipped cream canisters, and cartridges of the compressed gas are sold for use in whipped cream dispensers.

PHARMACOLOGY

Although chemically heterogeneous, inhalants are generally highly lipophilic compounds that gain rapid entrance into the central nervous system (CNS). Little is known about the cellular basis of the effects of inhalants and it is unclear whether these actually represent a single pharmacologic group. The

clinical effects of the volatile hydrocarbons are likely mediated through stimulation of γ-aminobutyric acid (GABA), although affects on the *N*-methyl-D-aspartate (NMDA) receptor are also described.

There are scant data on the pharmacokinetics of the inhalants. Factors determining pharmacokinetic and pharmacodynamic effects include concentration in inspired air; its partition coefficient; interaction with other inhaled substances, alcohol, and drugs; the patient's respiratory rate and blood flow; the patient's percent body fat; and individual variation in drug metabolism. The higher the blood-to-gas coefficient, the more soluble the substance is in blood. Substances with a low blood-to-gas partial coefficient, like nitrous oxide, are rapidly taken up by the brain and, conversely, are rapidly eliminated from the brain once exposure is ended (Table 79–1).

Inhalants are eliminated unchanged via respiration, undergo hepatic metabolism or both. Nitrous oxide and the aliphatic hydrocarbons are frequently eliminated unchanged in the expired air. The aromatic hydrocarbons are usually metabolized extensively via the cytochrome P450 (CYP) system, particularly CYP2E1, which has a substrate spectrum that includes a number of aliphatic, aromatic, and halogenated hydrocarbons.

Volatile Alkyl Nitrites

Unlike other volatile hydrocarbons, the volatile alkyl nitrites are not thought to have any direct effects on the CNS. Their effects are mediated through smooth muscle relaxation and they share a common cellular pathway with other nitric oxide (NO) donors, like nitroglycerin and sodium nitroprusside. Anesthetic uptake or induction, as well as emergence with N_2O, is rapid because of its low solubility in blood, muscle, and fat. There is no appreciable metabolism of N_2O in human tissue. An animal study found that N_2O significantly inhibited excitatory NMDA-activated currents and had no effect on GABA-activated currents.

CLINICAL MANIFESTATIONS

Signs and symptoms of inhalant use may be subtle, vary widely among individuals, and generally resolve within 2 hours of exposure. There may be a distinct odor on the patient's breath or clothing, as well as discoloration of skin around the nose and mouth. Mucous membrane irritation may cause sneezing, coughing, and tearing. Patients may complain of dyspnea and palpitations. Gastrointestinal complaints include nausea, vomiting, and abdominal pain. After an initial period of euphoria, patients may have residual headache and dizziness.

Volatile Hydrocarbons

Initial CNS effects include euphoria and hallucinations (both visual and auditory), as well as headache and dizziness. As toxicity progresses, CNS depression worsens and patients may develop slurred speech, confusion, tremor, and weakness. Transient cranial nerve palsies are reported. Further CNS depression is marked by ataxia, lethargy, seizures, coma, and respiratory depression. These acute effects generally resolve spontaneously.

Toxicity from chronic use is manifested most strikingly in the central nervous system. Leukoencephalopathy, characterized by dementia, ataxia, eye movement disorders, and anosmia, is the prototypical manifestation of chronic inhalant neurotoxicity. Neurobehavioral deficits include inattention,

TABLE 79–1. Blood:Gas Partition Coefficients, Routes of Elimination, and Important Metabolites of Selected Inhalants

Xenobiotic	Blood:Gas Partition Coefficient (98.6°F/37°C)	Routes of Elimination	Important Metabolites
Acetone	243–300	Largely unchanged via exhalation 95% and urine 5%	None
n-Butane	0.019	Largely unchanged via exhalation	None
Carbon tetrachloride	1.6	50% unchanged via exhalation; 50% hepatic metabolism and urinary excretion	CYP2E1 to trichloromethyl radical, trichloromethyl peroxy radical, phosgene
n-Hexane	2	10–20% exhaled unchanged; hepatic metabolism and urinary excretion	CYP2E1 to 2-hexanol, 2,5-hexanedione, γ-valerolactone
Methylene chloride	5–10	92% exhaled unchanged; hepatic metabolism and urinary excretion	(1) CYP2E1 to CO and CO_2 (2) Glutathione transferase to CO_2, formaldehyde, and formic acid
Nitrous oxide	0.47	>99% exhaled unchanged	None
Toluene	8–16	<20% exhaled unchanged; >80% hepatic metabolism and urinary excretion	CYP2E1 to benzoic acid, then (1) glycine conjugation to form hippuric acid (68%) (2) glucuronic acid conjugation to benzoyl glucuronide (insignificant pathway except following large exposure to toluene)
1,1,1-Trichloroethane	1–3	91% exhaled unchanged; hepatic metabolism and urinary excretion	CYP2E1 to trichloroethanol, then (1) conjugated wih glucuronic acid (urochloralic acid) or (2) further oxidized to trichloracetic acid
Trichloroethylene	9	16% exhaled unchanged; 84% hepatic metabolism and urinary excretion	CYP2E1 to epoxide intermediate (transient); chloral hydrate (transient); trichloroethanol (45%), trichloroacetic acid (32%)

apathy, and impaired memory and visuospatial skills with relative preservation of language.

Acute cardiotoxicity associated with hydrocarbon inhalation is manifested most dramatically in "sudden sniffer's death." The inhalant "sensitizes the myocardium" by blocking the potassium current (I_{Kr}), thereby prolonging repolarization. This produces a substrate for dysrhythmia propagation. Activity or stress then causes a catecholamine surge that initiates the dysrhythmia. Although cardiotoxic effects of inhalant abuse are generally acute, dilated cardiomyopathy is reported with chronic abuse of toluene and with trichloroethylene.

The primary respiratory complication of inhalational substance abuse is hypoxia, which is either a result of rebreathing of exhaled air, as occurs with bagging, or displacement of inspired oxygen with the inhalant, reducing the FiO_2. Direct pulmonary toxicity associated with inhalants is most often a result of inadvertent aspiration of a liquid hydrocarbon, producing acute lung injury. Irritant effects on the respiratory system are frequently transient, but patients may develop chemical pneumonitis, characterized by tachypnea, fever, tachycardia, rales/rhonchi, leukocytosis, and radiographic abnormalities. Barotrauma presents as pneumomediastinum or subcutaneous emphysema.

Hepatoxicity is associated with exposure to halogenated hydrocarbons, particularly carbon tetrachloride, as well as chloroform, trichloroethane, trichloroethylene, and toluene. Renal toxicity is most frequently described following inhalation of toluene. Production of hippuric acid, a toluene metabolite, is the most likely etiology for the nephrotoxicity. The excretion of abundant hippurate in the urine unmatched by ammonium mandates an enhanced rate of excretion of sodium and potassium cations. Continued loss of potassium in the urine leads to hypokalemia. Toluene is rapidly metabolized to hippuric acid, and the hippurate anion is swiftly cleared by the kidneys, leaving the hydrogen ion behind. This prevents the rise in anion gap that would normally occur with an acid anion other than chloride, generating a normal anion gap. Thus toluene abusing patients may present with profound hypokalemic muscle weakness.

Vesicular lesions resembling frostbite and massive, potentially life-threatening edema of the oropharyngeal, glottic, epiglottic and paratracheal structures are caused by the cooling of the gas associated with its rapid expansion once released from its pressurized container.

Methylene chloride, (dichloromethane), most commonly found in paint removers and degreasers, is unique among the halogenated hydrocarbons in that it undergoes metabolism in the liver by CYP2E1 to carbon monoxide. In addition to acute CNS and cardiac manifestations, inhalation of methylene chloride is associated with delayed onset and prolonged duration of signs and symptoms of carbon monoxide poisoning.

Methanol toxicity is reported following intentional inhalation of methanol-containing carburetor cleaners. Significant findings may include metabolic acidosis, CNS and respiratory depression, and blindness.

Chronic inhalation of the solvent *n*-hexane, a simple aliphatic hydrocarbon found in rubber cement among other places, may cause a sensorimotor peripheral neuropathy. Numbness and tingling of the fingers and toes is the most common initial complaint; progressive, ascending loss of motor function with quadriparesis may ensue.

Teratogenicity

Fetal solvent syndrome (FSS) was first reported in 1979 and is characterized by facial dysmorphia, growth retardation, and microcephaly, a constellation

of findings that resembles fetal alcohol syndrome. Compared to matched controls, infants born to mothers who report inhalant abuse are more likely to be premature, to be low birth weight, to have smaller birth length, and to have small head circumference. Followup studies of these infants show developmental delay compared to children matched for age, race, sex, and socioeconomic status.

Withdrawal

Observed similarities in the acute effects of inhalants compared with other CNS depressants have suggested similar patterns of tolerance and withdrawal. Symptoms include sleep disturbances, nausea, tremor, and irritability lasting 2–5 days after last use. Whether this represents a true withdrawal syndrome or residual effects of the inhalant is unclear.

Volatile Alkyl Nitrites

Methemoglobinemia caused by inhalation of amyl, butyl, and isobutyl nitrites is well reported. Patients may present with signs and symptoms of methemoglobinemia, including shortness of breath, cyanosis, tachycardia, and tachypnea.

Nitrous Oxide

Reported deaths associated with abuse of nitrous oxide (N_2O) appear to be a consequence of secondary effects of N_2O, including asphyxiation and motor vehicle collisions while under the influence, and not a consequence of direct toxicity. Chronic abuse of nitrous oxide is associated with neurologic toxicity mediated via irreversible oxidation of the cobalt ion of cobalamin (vitamin B_{12}). Myeloneuropathy resembles the subacute combined degeneration of the dorsal columns of the spinal cord of classic vitamin B_{12} deficiency. Presenting signs and symptoms reflect varying involvement of the posterior columns, the corticospinal tracts, and the peripheral nerves. Numbness and tingling of the distal extremities is the most common presenting complaint. Physical examination may reveal diminished sensation to pinprick and light touch, vibratory sensation and proprioception, gait disturbances, the Lhermitte sign (electric shock sensation with neck flexion), hyperreflexia, spasticity, urinary and fecal incontinence, and extensor plantar response.

LABORATORY AND DIAGNOSTIC TESTING

Routine urine toxicology screens are not capable of detecting inhalants or their metabolites. Most volatile agents are detectable using gas chromatography after exposure; the likelihood of detection is limited by the dose, time to sampling, and storage of the specimen. Blood is the preferred specimen, but urinalysis for metabolites such as hippuric acid (for toluene) may extend the time until the limit of detection is reached. Depending on the patient's signs and symptoms additional diagnostic testing may be indicated, including an electrocardiogram, chest radiograph, serum electrolytes, liver enzymes, and serum pH. The patient's presenting complaint(s) should guide decisions regarding further diagnostic testing.

MANAGEMENT

Management begins with assessment and stabilization of the patient's airway, breathing, and circulation. The patient should be connected to a pulse oxime-

ter and cardiac monitor. Oxygen should be administered and the patient should be treated with nebulized albuterol if wheezing is present. Early consultation with a regional poison control center may assist with identification of the toxin and patient management.

Cardiac dysrhythmias associated with inhalant abuse carry a poor prognosis. Life-threatening electrolyte abnormalities must be considered early and corrected in the patient presenting with dysrhythmias. Patients with nonperfusing rhythms should receive standard management with defibrillation. There are no evidence-based treatment guidelines for the management of inhalant-induced cardiac dysrhythmias, but agents with β-adrenergic antagonist activity are thought to offer some cardioprotective effects to the sensitized myocardium.

Other complications, including methemoglobinemia, elevated carboxyhemoglobin, and methanol toxicity, should be managed with the appropriate antidotal therapy. Patients with respiratory symptoms that persist beyond the initial complaints of gagging and choking should be evaluated for hydrocarbon pneumonitis and treated supportively. Agitation, either from acute effects of the inhalant or from withdrawal, is safely managed with a benzodiazepine. In the vast majority of patients, symptoms resolve quickly and hospitalization is not required.

80 Hallucinogens

EPIDEMIOLOGY

Hallucinogens are a diverse group of naturally occurring and synthetic drugs that alter and distort perception, thought, and mood without clouding the sensorium. Natural compounds have been used for thousands of years by many different cultures, largely during religious ceremonies. Synthetic hallucinogen use began with the discovery of lysergic acid diethylamide (LSD). The use of contemporary hallucinogens has grown in venues like all-night dance clubs and "rave parties."

SPECIFIC HALLUCINOGENS

The term *hallucination* may be defined as false perception that has no basis in the external environment. Hallucinations are distinct from illusions, which are misinterpretations of an actual experience. Hallucinogenic substances may also have illusogenic effects. Although the term *psychedelic* has been used for years, other terms, like entheogen and entactogen, frequently appear. Entheogens are "substances which generate the god or spirit within," whereas entactogens create an awareness of "the touch within."

The major structural classes of hallucinogens include the lysergamides, indolealkylamines (tryptamines), phenylethylamines (amphetamines), arylhexamines, cannabinoids, harmine alkaloids, and the tropane alkaloids. In addition, there are several unique hallucinogens, such as salvinorin A. This chapter focuses on lysergamides, tryptamines, phenylethylamines, and salvinorin A. Further discussion on the other classes of hallucinogens can be found in Chaps. 73, 81, 83, and 113.

Lysergamides

Lysergamides are derivatives of lysergic acid. Naturally occurring lysergamides are found in several species of morning glory (*Rivea corymbosa*, *Ipomoea violacea*) and Hawaiian baby wood rose (*Argyreia nervosa*). The synthetic lysergamide, LSD, is derived from an ergot alkaloid of the fungus, *Claviceps purpurea*. It is a water-soluble, colorless, tasteless, and odorless powder. LSD is typically sold as liquid-impregnated blotter paper, microdots, tiny tablets, "window pane" gelatin squares, liquid, powder, or tablets. The minimum effective oral dose is 25 μg, and typical street doses range from 20–80 μg. The onset of effects may occur 30–60 minutes after exposure, with a duration of effect of 10–12 hours. LSD users typically experience heightened awareness of auditory and visual stimuli with size, shape, and color distortions. The classic finding is a synesthesia, which is best described as a confusion of the senses. Users may describe "hearing colors" or "seeing sounds." Depersonalization and a sensation of enhanced insight or awareness can occur.

Indolealkylamines (Tryptamines)

Indolealkylamines, or tryptamines, represent a class of natural and synthetic compounds that structurally share a substituted monoamine group. Endogenous

tryptamines include serotonin and melatonin. Naturally occurring exogenous tryptamines include psilocybin, bufotenine, and dimethyltryptamine (DMT). Psilocybin is found in 3 major genera of mushrooms: *Psilocybe, Panaelous*, and *Conocybe* (Chap. 113). The effects of psilocin are similar to LSD, but with a shorter duration of action of about 4 hours. DMT is a potent short-acting hallucinogen and is used as an hallucinogenic "snuff." DMT is also a component of the hallucinogenic tea, Ayahuasca. In Ayahuasca, dimethyltryptamine-containing plants (eg, *Psychotria viridis*) are combined with plants containing harmine alkaloids (eg, *Banisteriopsis caapi*) that inhibit monoamine oxidases to increase the oral bioavailability of DMT. DMT is typically smoked, snorted, or injected. By this route, its hallucinogenic effects peak in 5–20 minutes, with a duration of 30–60 minutes. Certain species of the toad genus *Bufo* produce bufotenine, a tryptamine, and 5-methoxydimethyl tryptamine (or 5-Meo-DMT), as part of a complex defensive venom. The toad venom glands also produce cardioactive steroids, and death has resulted from overdose (Chap. 62).

Two of the more important synthetic tryptamines include *N,N*-diisopropyl-5-methoxytryptamine (5-Meo-DiPT, Foxy Methoxy), and α-methyltryptamine (AMT, IT-290). 5-Meo-DiPT is most commonly ingested, but may be smoked or insufflated. Effects begin 20–30 minutes after ingestion. The hallucinogenic effects are reported to last from 3–6 hours. AMT is a monoamine oxidase inhibitor that was initially marketed as an antidepressant in the former Soviet Union. Despite its chemical similarity to DMT, the effects of AMT can last from 12–16 hours.

Phenylethylamines (Amphetamines)

Endogenous phenylethylamines include dopamine, norepinephrine, and tyrosine. Exogenous phenylethylamines are known for their ability to stimulate catecholamine release and cause a variety of physiologic and psychiatric effects, including hallucinations. Methylenedioxymethamphetamine (MDMA), amphetamine, and methamphetamine are well-known members of this family and are discussed in detail in Chap. 73. The best recognized of the naturally occurring phenylethylamines is mescaline. Mescaline is found in peyote (*Lophophora williamsii*), a small, blue-green spineless cactus that grows in dry and rocky slopes throughout the southwestern United States and northern Mexico. Nausea, vomiting, and diaphoresis often precede the onset of hallucinations.

Salvia divinorum

Salvia divinorum is a perennial herb classified as a member of the mint family or *Labiatae*. Although there are more than 500 species of *Salvia*, only *S. divinorum* is recognized for its hallucinogenic properties. The plant may be chewed, smoked, or ingested as tea. Hallucinations occur nearly immediately after exposure and last only 1–2 hours. Synesthesias are reported.

PHARMACOKINETICS

LSD is the most studied hallucinogen, and there is extensive information about its pharmacokinetics. Plasma protein binding is more than 80% and volume of distribution is 0.28 L/kg. LSD has an elimination half-life of about 2.5 hours. Only small amounts are eliminated unchanged in the urine. Tolerance to the psychological effects of LSD occurs within 2 or 3 days following daily dosing,

but rapidly dissipates if the drug is withheld for 2 days. Psychological cross-tolerance among mescaline, psilocybin, and LSD is reported in humans. There is no evidence for physiologic tolerance, physiologic dependence, or a withdrawal syndrome with LSD. Limited tolerance is demonstrated between psilocybin and cannabinoids such as marijuana.

PHARMACOLOGY

Although the lysergamide, indolealkylamine, and phenylethylamine hallucinogens are structurally distinct, studies support a common site of action on central serotonin (5-HT) receptors. The 5-HT_{2A} receptor is the most likely common site of hallucinogen action. The lysergamide, indolealkylamine, and phenylethylamine hallucinogens all bind to the 5-HT_2 class of receptors. There is a good correlation between the affinity of both indolealkylamine and phenylethylamine hallucinogens for 5-HT_2 receptors in vitro and hallucinogenic potency in humans in vivo.

CLINICAL EFFECTS

Physiologic changes accompany and often precede the perceptual changes induced by hallucinogens. The physical effects may be caused by direct drug effect or by a response to the disturbing or enjoyable hallucinogenic experience. Sympathetic effects are variable and include mydriasis, tachycardia, hypertension, tachypnea, hyperthermia, and diaphoresis. Other reported clinical findings include piloerection, dizziness, hyperactivity, muscle weakness, ataxia, altered mental status, coma, and hippus, a rhythmic dilation and constriction of the pupils. Nausea and vomiting often precede the psychedelic effects produced by psilocybin and mescaline.

Potentially life-threatening complications, such as hyperthermia, coma, respiratory arrest, hypertension, tachycardia, and coagulopathy, can occur following a *massive* LSD overdose. The vast majority of morbidity from hallucinogen use is associated with trauma.

The psychological effects of hallucinogens are dose related and affect changes in arousal, emotion, perception, thought process, and self-image. The response to the drug is related to the user's mindset, emotions, or expectations at the time of exposure, and can be altered by the group or setting. Perceptual distortions are common, typically involving distortion of body image and alteration in visual perceptions. Acute adverse psychiatric effects of hallucinogens include panic reactions, true hallucinations, psychosis, and major depressive dysphoric reactions. Acute panic reaction, the most common adverse effect, presents with frightening illusions, tremendous anxiety, apprehension, and a terrifying sense of loss of self-control.

LABORATORY

Routine drug-of-abuse screens do not detect LSD or other hallucinogens. Although LSD exposure can be detected by more sophisticated testing, these tests are not valuable in the clinical setting. Depending on their structure, phenylethylamines may cause positive qualitative urine testing for amphetamines.

TREATMENT

Most hallucinogen users do not seek medical attention because they experience only the desired effect of the drug. For any hallucinogen user who does

present to the emergency department, initial treatment must begin with attention to airway, breathing, circulation, level of consciousness, and abnormal vital signs. Even when hallucinogen exposure is suspected, the basic approach to altered mental status should include consideration of dextrose, thiamine, naloxone, and oxygen therapy as indicated, along with a vigorous search for other etiologies.

Hallucinogens rarely produce life-threatening toxicity. Sedation with benzodiazepines is usually sufficient to treat hypertension, tachycardia, and hyperthermia. Benzodiazepines remain the cornerstone of therapy, as the sedating effect can diminish both endogenous and exogenous sympathetic effects. Hyperthermia requires urgent sedation with benzodiazepines and rapid cooling.

Gastrointestinal decontamination with activated charcoal may be considered for asymptomatic patients with recent ingestions, but is probably not helpful after clinical symptoms appear, and attempts to use it may lead to further agitation. Excessive physical restraint should be avoided out of concern for hyperthermia and rhabdomyolysis.

Serotonin syndrome can occur after hallucinogen use, and has been described after LSD, tryptamine, and phenylethylamine use. Specific therapy with cyproheptadine may be warranted (Chap. 70).

LONG-TERM EFFECTS

Long-term consequences of LSD use include prolonged psychotic reactions, severe depression, and exacerbation of preexisting psychiatric illness. Flashbacks have been reported in 15–80% of LSD users. Anesthesia, alcohol intake, and medications can precipitate flashbacks. These abnormal perceptions can be triggered during times of stress, illness, and exercise, and are often a virtual recurrence of the initial hallucinations. Hallucinogen-persisting perception disorder (HPPD) is a chronic problem associated with LSD abuse. According to the *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition (DSM-IV), the diagnosis of HPPD requires the recurrence of perceptual symptoms that were experienced while intoxicated with the hallucinogen that causes functional impairment and is not a result of a medical condition. Symptoms are primarily visual, and reality testing is typically intact in HPPD. One finding described after LSD use is palinopsia, or "trailing," which refers to the continued visual perception of an object after it has left the field of vision.

Although many drugs have been tried to treat patients with HPPD, most have not proven beneficial. Clonazepam reportedly improves, and haloperidol and risperidone exacerbate, panic and visual symptoms.

81 Cannabinoids

Cannabis is a collective term referring to the bioactive substances from *Cannabis sativa*. In this chapter, the term *cannabis* is used to encompass all cannabis products. The *Cannabis sativa* plant contains a group of more than 60 chemicals called cannabinoids. The major cannabinoids are cannabinol, cannabidiol, and tetrahydrocannabinol. The principal psychoactive cannabinoid is Δ^9-tetrahydrocannabinol (THC). Marijuana is the common name for a mixture of dried leaves and flowers of the plant. Hashish and hashish oil are the pressed resin and the oil expressed from the pressed resin, respectively. The concentration of THC varies from 1% in low-grade marijuana up to 50% in hash oil. Pure THC and a synthetic cannabinoid are available as prescription drugs with the generic names of dronabinol and nabilone, respectively.

HISTORY AND EPIDEMIOLOGY

Cannabis has been used for more than 4000 years. The earliest documentation of the therapeutic use of marijuana is the 4th century B.C. in China. Currently, marijuana is the most commonly used illicit drug in the United States. A recent study by the Substance Abuse and Mental Health Services Administration reported that 95 million persons 12 years old and older (40% of that population) had tried marijuana at least once. Approximately 14.6 million persons used marijuana in the month prior to the survey, of whom 4.8 million persons used it on ≥20 days in that month.

PHARMACOLOGY AND PATHOPHYSIOLOGY

Cannabinoids have been proposed for use in the management of many clinical conditions, but have only been approved for the control of chemotherapy-related nausea and vomiting resistant to conventional antiemetics, for breakthrough postoperative nausea and vomiting, and for appetite stimulation in HIV patients with anorexia-cachexia syndrome.

In the early 1990s, two specific cannabinoid-binding receptors were identified: CB1 (or *Cnr1*) and CB2 (or *Cnr2*). Subsequent research identified endogenous cannabinoid receptor ligands (anandamide, palmitoylethanolamide) as well as cannabinoid receptor agonists and antagonists.

CB1 receptors are distributed throughout the brain with high densities in the basal ganglia, substantia nigra, globus pallidus, cerebellum, hippocampus, and cerebral cortex (particularly the frontal regions). CB2 receptors are located peripherally in immune system tissues (spleen, macrophages), peripheral nerve terminals, and the vas deferens. Both receptors inhibit adenyl cyclase and stimulate potassium channel conductance. CB1 receptors are located on the presynaptic side of central nervous system synapses and activation of them inhibits the release of acetylcholine, L-glutamate, γ-aminobutyric acid, noradrenaline, dopamine, and serotonin.

The neuropharmacologic mechanisms by which cannabinoids produce their psychoactive effects have not been fully elucidated. Nevertheless, activity at the CB1 receptors is believed to be responsible for the clinical effects of cannabinoids, including the regulation of cognition, memory, motor activities, nociception, and nausea and vomiting.

PHARMACOKINETICS AND TOXICOKINETICS

Absorption

Inhalation of smoke containing THC results in the onset of psychoactive effects within minutes. From 10–35% of available THC is absorbed during smoking and peak concentrations of THC occur an average of 8 (range: 3–10) minutes after the onset of smoking marijuana. Peak plasma concentrations depend on the dose, but a marijuana cigarette containing 1.75% THC produces a peak plasma THC concentration of approximately 85 ng/mL. Ingestion of cannabis results in an unpredictable onset of psychoactive effects in 1–3 hours. Because of the instability of THC in acidic gastric fluid and first-pass hepatic clearance, only 5–20% of available THC reaches the systemic circulation following ingestion. Peak plasma concentrations of THC usually occur 2–4 hours after ingestion, but delays up to 6 hours are described.

Dronabinol has an oral bioavailability of approximately 10% and peak plasma concentrations occur 2–3 hours after ingestion. Nabilone has an oral bioavailability greater than 90% and reaches peak plasma concentrations 2 hours after ingestion. The therapeutic plasma concentration of THC for the treatment of nausea and vomiting is greater than 10 ng/mL.

Distribution

THC has a steady-state volume of distribution of approximately 2.5–3.5 L/kg and is 98% bound, primarily to plasma lipoproteins. Cannabinoids are lipid-soluble and accumulate in fatty tissue in a biphasic pattern.

Metabolism

THC is nearly completely metabolized by hepatic microsomal hydroxylation and oxidation by the cytochrome P450 system (primarily CYP2C9). The primary metabolite (11-hydroxy-Δ^9-THC or 11-OH-THC) is active and is subsequently oxidized to the inactive 11-nor-Δ^9-THC carboxylic acid metabolite (THC-COOH) and many other metabolites.

Excretion

Reported plasma elimination half-lives of THC and its major metabolites vary considerably. Following intravenous doses of THC, the mean elimination half-life ranges from 1.6–57 hours. Plasma elimination half-lives are expected to be similar following inhalation. In the 72 hours following ingestion, approximately 15% of a THC dose is excreted in the urine, and roughly 50% is excreted in the feces. Following intravenous administration, approximately 15% of a THC dose is excreted in the urine and only 25–35% is excreted in the feces. Inhalation is expected to produce results similar to intravenous administration. In 5 days, 80–90% of a THC dose is excreted from the body.

Following discontinuation of use, metabolites may be detected in the urine of chronic users for several weeks. Factors such as age, weight, and use more than once a day only partially explain the long excretion period.

CLINICAL MANIFESTATIONS

The clinical effects of THC use, including time of onset and duration of effect, vary with the dose, the route of administration, the experience of the

user, the vulnerability of the user to psychoactive effects, and the setting in which the drug is used.

Psychological Effects

The most commonly self-reported effect is relaxation. Other commonly reported effects are perceptual alterations (heightened sensory awareness, slowing of time), a feeling of well-being (including giddiness or laughter), and increased appetite.

Physiologic Effects

Social use of cannabis is associated with physiologic effects on cerebral blood flow, the heart, the lungs, and the eyes. THC increases cerebral blood flow, particularly in the frontal cortex, insula, cingulate gyrus, and subcortical regions, 30–60 minutes after dosing and continuing for at least 120 minutes. Common acute cardiovascular effects of cannabis use include increases in heart rate and decreases in vascular resistance. Decreased vascular tone may cause postural hypotension accompanied by dizziness and syncope. Inhalation or ingestion produces a dose-related short-term decrease in airway resistance and an increase in airway conductance in normal and in asthmatic individuals that reaches a peak at 15 minutes and lasts 60 minutes; ingestion of cannabis produces a significant increase in airway conductance at 30 minutes, which peaks at 3 hours and lasts 4–6 hours. The principal ocular effects of cannabis are conjunctival injection and decreased intraocular pressure. Neurologic effects may include decreases in coordination, muscle strength, and hand steadiness. Lethargy, sedation, inability to concentrate, slurred speech, and slowed reaction time also may occur. Cannabis users occasionally may experience distrust, dysphoria, fear, panic reactions, or transient psychotic episodes.

In young children, the acute ingestion of cannabis is potentially life-threatening. Ingestion by children of estimated amounts of 250–1000 mg of hashish resulted in obtundation in 30–75 minutes. Tachycardia (>150 beats/min) was found in one-third of the children. Less commonly reported findings included apnea, cyanosis, bradycardia, hypotonia, and opisthotonus.

Chronic Use Adverse Effects

Long-term use of cannabis is associated with a number of adverse effects. Cannabinoids affect host resistance to infection by modulating the secondary immune response (macrophages, T and B lymphocytes, acute phase and immune cytokines). However, an immune-mediated health risk from using cannabis has not been documented. Smoking marijuana delivers more particulates to the lower respiratory tract than smoking tobacco. Cancer of the respiratory tract appears to be associated with the regular smoking of marijuana, although exposure to tobacco smoke may be a confounding factor. Reduced fertility in chronic users is a result of oligospermia, abnormal menstruation, and decreased ovulation. Cannabis is a category C drug in pregnancy and affects birth weight and length, but does not cause fetal malformations. Epidemiologic studies based on self-reporting of cannabis use do not support an association between the use of cannabis during pregnancy and teratogenesis.

There is a concern that chronic cannabis use results in deficits in cognition and learning that last well after cannabis use has stopped. An amotivational

syndrome is also attributed to cannabis use. The syndrome is a poorly defined complex of characteristics such as apathy, underachievement, and lack of energy and may be related to depression.

Chronic daily use of cannabis creates dependence although the amount, frequency, and duration of use required to develop dependence are not well established. Much of the support for cannabis dependence is based on the existence of a withdrawal syndrome. The most reliably reported symptoms are irritability, restlessness, nervousness, and appetite and sleep disturbances. Other reported withdrawal manifestations include tremor, diaphoresis, fever, and nausea.

DIAGNOSTIC TESTING

Cannabinoids can be detected in plasma or urine. Enzyme-multiplied immunoassay technique (EMIT) and radioimmunoassay (RIA) are routinely available; gas chromatography–mass spectrometry (GC-MS) is the most specific assay and is used as the reference method.

EMIT is a qualitative urine test that is often used for screening purposes. EMIT identifies the major metabolites of THC. In these tests, the concentrations of all metabolites present are additive. Qualitative urine test results do not indicate or measure intoxication or degree of exposure. The National Institute on Drug Abuse guidelines for urine testing specify test cutoff concentrations of 50 ng/mL for screening and 15 ng/mL for confirmation. Metabolites may be detected in the urine for 72–96 hours following a single marijuana cigarette, whereas in heavy users, urine tests may be positive for several weeks after last use.

MANAGEMENT

Gastrointestinal decontamination is not recommended for patients who ingest cannabis products, nabilone, or dronabinol because clinical toxicity is rarely serious and, if present, responds to supportive care. In addition, a patient with a significantly altered mental status (eg, somnolence, agitation, anxiety) has risks associated with gastrointestinal decontamination that outweigh the potential benefits of the intervention.

Adverse psychological effects (eg, agitation, anxiety, transient psychotic episodes) should be treated with quiet reassurance and benzodiazepines (lorazepam 1–2 mg IM or diazepam 5–10 mg IV), as needed. There are no specific antidotes for cannabis. The effects of coingestants, such as cocaine or ethanol, should be identified or anticipated and treated as indicated.

82 Nicotine and Tobacco Preparations

HISTORY AND EPIDEMIOLOGY

It is widely accepted that tobacco is addictive and that nicotine is the component primarily responsible for dependency.

Fifty million Americans, representing 25% of the adult population, smoke cigarettes. In the United States, 350,000 deaths annually are attributable to cigarette smoking, making it the single most important cause of preventable premature mortality. The principal sources of nicotine exposure and poisoning are tobacco products (cigarettes, cigars, pipe tobacco, chewing tobacco, and snuff) and smoking-cessation products (such as nicotine gum, patches, nasal and oral sprays, and lozenges). Nicotine had a brief application as an animal tranquilizer and nicotine salts were used extensively as an agricultural insecticide in the 1920s and 1930s; formulations of this product are still used by "organic" gardeners.

Sources of Nicotine

The total nicotine content of a "regular" American cigarette varies between 13 and 20 mg. "Low nicotine" cigarettes contain half this amount, and many European cigarettes contain up to 30 mg of nicotine. When a cigarette is smoked, only 0.5–2.0 mg of nicotine is delivered to the smoker. Smokers vary this amount by altering the rate of puffing, the puff volume, the depth and duration of inhalation, and the size of the residual butt. Table 82–1 lists the nicotine contents and delivered amounts of various products.

Green leaf tobacco sickness (GTS) occurs when a tobacco harvester handles dew-laden tobacco leaves. The nicotine dissolves in the water and is absorbed through the worker's skin, if cutaneous precautions are not taken.

PHARMACOLOGY AND PHARMACOKINETICS

Nicotine, a tertiary amine, is a colorless, bitter-tasting, and highly water-soluble volatile liquid that is weakly alkaline (pK_a = 8.0–8.5). The principal source of nicotine is the tobacco plant, *Nicotiana tabacum*, but it can also be isolated from *Nicotiana rustica,* and in smaller quantities in plants outside the *Nicotiana* genus. Alkaloids with chemical structures and physiologic activity similar to that of nicotine include lobeline, derived from *Lobelia inflata*, cystisine, found in mescal beans, and coniine, the lethal alkaloid in "poison hemlock."

Table 82–2 summarizes the pharmacologic characteristics of nicotine.

Drug Interactions

A number of studies demonstrate that smokers have altered metabolism of many commonly used medications via autoinduction. The compounds listed in Table 82–3 metabolize more quickly than in nonsmokers.

PATHOPHYSIOLOGY

Nicotine binds to select acetylcholine receptors, known as nicotine receptors. These receptors are located throughout the body, particularly in the auto-

TABLE 82–1. Sources of Nicotine

Source	Content (mg)	Delivered (mg)[a]
1 whole cigarette	13–30	0.5–2.0
1 low-yield cigarette	3–8	0.1–1.0
1 cigarette butt	5–7	—
1 cigar	15–40	0.2–1.0
1 g of snuff (wet)	12–16	2.0–3.5
1 g of chewing tobacco	6–8	2.0–4.0
1 piece of nicotine gum	2 or 4	1.0–2.0
1 nicotine patch	8.3–114	5.0–22/24 h
1 nicotine nasal spray	0.5	0.2–0.4

[a]Delivered through intended use of standard dose.

nomic ganglia, adrenal medulla, central nervous system, spinal cord, neuromuscular junctions, and chemoreceptors of the carotid and aortic bodies. Nicotinic receptors at neuromuscular junctions are part of a Na^+ channel. Stimulation of these receptors results mainly in Na^+ influx, depolarization of the endplate, and triggering of an action potential that is propagated down muscle by voltage-gated Na^+ channels.

Nicotinic receptors on central or peripheral neurons or in the adrenal gland are also ion channels. In some cases Ca^{2+} influx through the receptor may be more important than Na^+ influx.

Agents that bind to and activate nicotinic receptors may stimulate postganglionic sympathetic and parasympathetic neurons, skeletal muscle endplates, and neurons within the CNS. Prolonged depolarization at the receptor eventually causes blockade of nicotinic receptors, producing the biphasic clinical syndrome described. Thus hypertension, tachycardia, vomiting, diarrhea, muscle fasciculations, and convulsions (excitation) are followed by hypotension, bradydysrhythmias, paralysis, and coma (blockade).

CLINICAL MANIFESTATIONS

Most reported acute nicotine exposures produce no toxicity because of the low doses involved with unintentional exposures. Nonetheless, serious exposures do occur. A child who ingests one or more cigarettes or three or more cigarette butts has a 90% chance of becoming symptomatic. Conversely, ingestion of smaller amounts will produce symptoms only half the time. As little as 1 mg of nicotine can produce symptoms in a small child; 4–8 mg of nicotine might produce symptoms in an adult, especially a nonhabituated victim, and a lethal dose might be on the order of 40–60 mg.

TABLE 82–2. Pharmacologic Characteristics of Nicotine

Absorption	Lungs, oral mucosa, skin, intestinal tract, gastric acidity inhibits absorption
Volume of distribution	~ 1 L/kg
Protein binding	5–20%
Metabolism	80–90% hepatic, remainder in lung and kidney; principle metabolites are cotinine, nicotine-1'-*N*-oxide
Half-life	1–4 h, shorter in smokers (average, 2h); half-life of cotinine is 19 h
Elimination	2–35% excreted unchanged in urine

TABLE 82–3. Xenobiotics with Enhanced Metabolism in Smokers

β-Adrenergic antagonists	Nicotine
Benzodiazepines	Opioids
Caffeine	Phenacetin
Cyclic antidepressants	Theophylline
Histamine (H_2) antagonists	

Vomiting is the most common symptom of nicotine poisoning, occurring in more than 50% of symptomatic patients. However, it is not entirely reliable as patients can present with lethargy and respiratory depression without prior vomiting or any other signs of CNS stimulation. Moreover, nicotine chewing gum ingestions in children produce vomiting less frequently (20% incidence) than do those with cigarette ingestions. Following the ingestion of tobacco products, children usually manifest symptoms within 30–90 minutes. When children chew nicotine gum, symptoms are usually apparent within 15–30 minutes, a result of more rapid absorption through the buccal mucosa. When death occurs, it usually occurs within 1 hour of exposure. With mild poisonings, symptoms generally last only 1–2 hours after exposure. With severe toxicity, however, full recovery might take 48–72 hours.

Table 82–4 outlines the symptoms associated with acute nicotine exposure. The symptoms may follow a biphasic pattern in which there is initial stimulation followed quickly by inhibition.

DIAGNOSTIC TESTING

Toxicologic assay for nicotine or its metabolites is of limited value in the management of a patient with an acute poisoning. A serum nicotine concentration greater than 50 ng/mL generally predicts serious toxicity, but lower concentrations can also be significant in the nontolerant patient. The presence of nicotine or cotinine in the urine might reflect coincidental active or passive smoke exposure and therefore does not confirm nicotine as the cause of poisoning.

MANAGEMENT

Unintentional ingestions of nicotine in small children almost invariably involve small amounts, with spontaneous vomiting providing adequate decontamination. Individuals who ingest one or more whole cigarettes or three or more cigarette butts or who acquire their exposures from a more toxic source should be given activated charcoal if not otherwise contraindicated. If vomiting has not occurred following a significant recent oral exposure, orogastric lavage should be considered prior to activated charcoal administration. Because nicotine undergoes enteroenteric or enterohepatic circulation, multiple-dose activated charcoal should be considered in patients with serious exposures. In cases of skin exposure to wet tobacco leaves, concentrated nicotine liquid, or nicotine pesticide powder, the patient's clothing should be promptly removed, bagged, and not returned to the patient, and the skin thoroughly washed with soap and water. The medical staff must wear impervious gloves and gowns during these procedures to avoid secondary exposure.

Symptom-Directed Treatment

Treatment of nicotine toxicity is a complex therapeutic problem and should be based on a symptom analysis with primary emphasis on respiratory sup-

TABLE 82–4. Signs and Symptoms of Acute Nicotine Poisoning

	Gastrointestinal	Respiratory	Cardiovascular	Neurologic	
Early (15–60 min)	Abdominal pain Nausea Salivation Vomiting	Bronchorrhea Hyperpnea	Hypertension Tachycardia Pallor	Agitation/anxiety Ataxia/dizziness Blurred vision Confusion Distorted hearing	Headache Hyperactivity Muscle fasciculations Seizures Tremors
Delayed (0.5–4 h)	Diarrhea	Apnea Hypoventilation	Bradycardia Dysrhythmias Hypotension Shock	Coma Hyporeflexia Hypotonia	Lethargy Weakness Muscle paralysis

port. Seizures are usually treated with a benzodiazepine. Loading the patient with longer-acting anticonvulsants is generally unnecessary. Cardiovascular compromise is treated with atropine for symptomatic bradycardia and fluids for hypotension. If hypotension does not respond to fluids, a vasopressor, such as dopamine or norepinephrine, is recommended. Respiratory compromise, caused by respiratory depression, is generally treated with oxygen, intubation, and positive pressure ventilation as indicated.

Enhancing Elimination

Although nicotine is a weak base (pK_a = 8.0–8.5) and excretion can theoretically be enhanced by acidification of the urine, this approach is to be avoided, because the potential risks of acidification in a patient with seizures and possible rhabdomyolysis outweigh any of the theoretical benefits.

83 Phencyclidine and Ketamine

HISTORY AND EPIDEMIOLOGY

Phencyclidine (PCP) was discovered in 1926, but it was not developed as a general anesthetic until the 1950s. The use of PCP in surgery began in 1963, but PCP was rapidly discontinued following the frequent development of postoperative psychoses and dysphoria. Simultaneously, PCP was developing as a street drug called "the PeaCe Pill." Phencyclidine abuse became widespread during the 1970s. The relatively easy and inexpensive synthesis coupled with the common masking of PCP as lysergic acid diethylamide (LSD), mescaline, psilocybin, cocaine, amphetamine, and/or "synthetic THC" (tetrahydrocannabinol) added to its allure and consumption. The legal manufacture of phencyclidine was ultimately prohibited in 1978, when the drug was added to the list of federally controlled substances. Because many PCP congeners made during the manufacturing process were being abused in place of PCP, the Controlled Substance Act of 1986 made these derivatives illegal and established that the use of piperidine, the precursor of PCP, necessitated mandatory reporting.

Laboratory investigation of phencyclidine derivatives led to the discovery of ketamine, which was introduced for clinical practice in 1970. Ketamine ("special K") abuse was first noted in 1971. Ketamine is not manufactured illegally, but instead is diverted illicitly from legitimate medical, dental, and veterinary sources. Ketamine use has increased throughout the last 15 years in spite of the common complications associated with its use. Ketamine is regularly consumed at all-night "rave parties" and in nightclubs because of its "hallucinatory" and "out-of-body" effects, limited expense, and short duration of effect (a single snort lasting 15–20 minutes).

PHARMACOLOGY

More than 60 psychoactive analogs of PCP are mentioned in the medical literature. Although potencies vary, the clinical manifestations of the most common analogs are virtually identical. Ketamine is the only dissociative anesthetic manufactured for human use.

The molecular structure of ketamine contains a chiral center, producing a racemic mixture of the D(+) and the L(–) isomer. Although commercially available preparations of ketamine contain equal concentrations of the two enantiomers, the D(+)-isomer of ketamine is a more effective anesthetic, but also has a higher incidence of emergence reactions.

Phencyclidine is a weak base with a pK_a between 8.6 and 9.4 and a high lipid-to-water partition coefficient. It is rapidly absorbed from the respiratory and the gastrointestinal tracts; as such, it is typically self-administered by oral ingestion, nasal insufflation, smoking, and intravenous and subcutaneous injection.

The effects of PCP are dependent on routes of delivery and dose. Its onset of action is most rapid from the intravenous and inhalational routes (2–5 minutes) and slowest (30–60 minutes) following gastrointestinal absorption. Sedation is commonly produced by doses of 0.25 mg intravenously, whereas oral ingestion typically requires 1–5 mg to produce similar sedation. Signs

and symptoms of toxicity usually last 4–6 hours and large overdoses generally resolve within 24–48 hours. PCP has a large volume of distribution (6.2 L/kg) and is stored in the adipose and brain tissue. Also upon reaching the acidic cerebrospinal fluid (CSF), PCP becomes ionized and trapped, producing CSF levels approximately 6–9 times higher than those of plasma.

PCP undergoes first-order elimination over a wide range of doses. It has an apparent terminal half-life of 21 ± 3 hours under both controlled and overdose settings. Ninety percent of PCP is metabolized in the liver and 10% is excreted in the urine unchanged. Urine pH is an important determinant of renal elimination of PCP. In acidic urine, PCP becomes ionized and then cannot be reabsorbed. Acidification of the urine increases renal clearance of PCP from 1.98 ± 0.48 L/h to 2.4 ± 0.78 L/h. Although this may account for a 23% increase in the renal clearance, this only represents a 1.1% increase of the total drug clearance.

Similarly, ketamine is water soluble with a high lipid solubility that enables it to distribute to the CNS readily. It has a pK_a of 7.5 and a volume of distribution of 1.8 ± 0.7 L/kg. Ketamine has approximately 10% of the potency of PCP. Peak concentrations occur within 1 minute of IV administration and within 5 minutes of a 5 mg/kg IM injection. Recovery time averages 15 minutes for IV administration, but it is prolonged to between 30 and 120 minutes for intramuscular administration. Oral or rectal doses are not well absorbed and undergo substantial first-pass metabolism. In contrast to oral administration of ketamine where symptoms last 4–8 hours, symptoms after nasal administration last 45–90 minutes.

Ketamine is extensively metabolized in the liver. The elimination half-life, which reflects both metabolic and excretory phases, is 2.3 ± 0.5 hours and is prolonged when drugs requiring hepatic metabolism are coadministered.

PATHOPHYSIOLOGY

The mechanisms by which PCP and ketamine functionally and electrophysiologically "dissociate" the somatosensory cortex from higher centers are complex and not fully understood. PCP and ketamine block the *N*-methyl-D-aspartate (NMDA) receptors and bind to the biogenic amine reuptake complex with 10–20% of the affinity to which they bind to the NMDA receptor. This weak inhibition of the catecholamine and dopamine reuptake accounts for the respective sympathomimetic and psychomotor effects. In significant overdoses, PCP and ketamine also stimulate σ-receptors at concentrations generally associated with coma, although with lower affinity than NMDA receptors. At higher concentrations typically associated with death, PCP and ketamine also bind to the nicotinic, opioid, and muscarinic cholinergic receptors.

PCP induces modest tolerance and dependence in animal models. Physiologic dependence in humans has not been studied formally, although it is implied to occur.

CLINICAL MANIFESTATIONS

The reported variations in signs and symptoms of PCP toxicity are a result of differences in dosage, the multiple routes of administration, concomitant drug use, and other associated medical conditions. In addition, individual differences in susceptibility to the effect of the drug, the development of toler-

ance in chronic users, as well as contaminants in the drug manufacture can account for erratic clinical findings.

Vital Signs

Body temperature is rarely affected directly by PCP and ketamine. When hyperthermia does occur, all the known complications, including encephalopathy, rhabdomyolysis, myoglobinuria, electrolyte abnormalities, and liver failure, occur. Most PCP- and ketamine-toxic patients demonstrate mild sympathomimetic effects. PCP consistently increases both systolic and diastolic blood pressure in a dose-dependent fashion. PCP also increases the heart rate, although inconsistently. Likewise, ketamine produces mild increases in blood pressure, heart rate, and cardiac output via this same mechanism.

Cardiopulmonary

Rarely complications can result from direct vasospasm of blood vessels causing severe hypertension and cerebral hemorrhage. Dysrhythmias are observed in animals poisoned with very large doses of PCP or ketamine. The considerable experience in the use of ketamine anesthesia on humans undergoing surgery or cardiac catheterizations has not demonstrated prodysrhythmic effects.

As these dissociative anesthetics were designed to retain normal ventilation, hypoventilation is uncommon. Clinically, PCP-toxic patients, have irregular respiratory patterns, with tachypnea much more common than bradypnea. Hypoventilation, when present, is usually secondary to particularly high doses of PCP. Although respiratory depression in humans is an extremely rare event, it has been reported with fast or high-dose infusions of ketamine as well.

Neuropsychiatric and Psychomotor

The majority of patients with PCP and ketamine toxicity who are brought to medical attention manifest diverse psychomotor abnormalities. These drugs produce a lack of response to external stimuli by dissociating various elements of the mind. Clinically, the person may appear inebriated, either calm or agitated, and sometimes violent. In large overdoses, the anesthetic effect of the drug causes patients to develop stupor or coma. Both drugs also cause feelings of apathy, depersonalization, hostility, isolation, and alterations in body image. Hallucinations are typically auditory rather than visual, which are more common with LSD use. The majority of ketamine users report experiencing a "k-hole," a slang term for the intense psychological and somatic state experienced while under the influence of ketamine. This experience varies with the individual, but can include buzzing, ringing or whistling sounds, traveling through a dark tunnel, intense visions, and out-of-body or near-death sensations.

Typically, neurologic signs include rotatory nystagmus, ataxia, and altered gait. Initially, except for ataxia, motor movement is not impaired, until the patient becomes unconscious. Pupils are typically relatively small. Myoclonic movements, tremor, hyperactivity, athetosis, stereotypies, and catalepsy also occur.

Emergence Reaction

The acute psychosis, observed during the recovery phase of PCP anesthesia, limits its clinical use. This bizarre behavior, characterized by a confused state, vivid dreaming, and hallucinations, is termed an "emergence reaction." These same postanesthetic reactions also limit the clinical use of ketamine.

Patients older than 10 years of age, women, and those who normally dream frequently and/or have a prior personality disorder incur the greatest risk.

DIAGNOSTIC TESTING

Most hospital laboratories do not perform quantitative analysis of PCP, but many can do a qualitative urine test for the presence of the drug. Rarely is it essential to make this determination as a negative test does not exclude the use of one of PCPs many congeners. Because of its similar structure to PCP, dextromethorphan and its metabolite dextrorphan cross-react with some common assays for PCP. There is also anecdotal evidence that ketamine may occasionally cross-react with the urine PCP immunoassays.

Although nonspecific, laboratory findings resulting from PCP or ketamine use may include leukocytosis, hypoglycemia, and elevation of muscle enzymes, myoglobin, BUN, and creatinine.

MANAGEMENT

Agitation

Conservative management is indicated for PCP and ketamine toxicity, and includes maintaining adequate respiration, circulation, and thermoregulation. The psychobehavioral symptoms observed during acute dissociative reactions and during the emergence reaction are similar. To prevent self-injury, a common form of PCP-induced morbidity and mortality, the patient must be safely restrained, initially physically and then chemically. Pharmacologic treatment for psychomotor agitation should be accomplished immediately with adequate sedation to control motor activity. A benzodiazepine, such as diazepam, administered in titrated doses of up to 10 mg intravenously every 5–10 minutes until agitation is controlled, is usually safe and effective. The use of dextrose and 100 mg of thiamine HCl intravenously should be considered as clinically indicated. Rapid immersion in an ice water bath may be necessary if body temperature is greater than 106°F (41.1°C).

Decontamination

Patients with a history of recent oral use of PCP are candidates for gastrointestinal decontamination, but they should be considered too unstable for induced emesis, as uncontrolled agitation or respiratory compromise can rapidly develop. Although there is rarely, if ever, an indication for orogastric lavage unless a significant coingestant is suspected. Activated charcoal, 1 g/kg, should be administered as soon as possible, and repeated every 4 hours for several doses. Activated charcoal effectively adsorbs PCP and increases its nonrenal clearance. Even without prior gastric evacuation, this approach is usually adequate.

Theoretically, PCP can be eliminated more rapidly if the urine is acidified. We do not recommend this approach, however, because of the risks associated with acidifying the urine and the limited theoretical or clinical benefits. Continuous gastric suctioning, may also be dangerous and unnecessary.

Supportive Care

The major toxicity of PCP appears to be behaviorally related: self-inflicted injuries, injuries resulting from exceptional physical exertion, and injuries

sustained as a result of resisting the application of physical restraints are frequent. Patients appear to be unaware of their surroundings, and sometimes even oblivious to pain, because of the dissociative anesthetic effects. In addition to major trauma, rhabdomyolysis and resultant myoglobinuric renal failure account in large measure for the high morbidity and mortality associated with PCP toxicity.

If significant rhabdomyolysis has occurred, myoglobinuria may be present. Early fluid therapy should be used to avoid deposition of pigment into the kidneys, leading to renal failure. Urinary alkalinization as part of the treatment regimen for rhabdomyolysis, would potentially increase PCP reabsorption and deposition in fat stores, but this concern is only theoretical. Although the clinical experience with recreational use of ketamine and dextromethorphan are limited, their manifestations appear to be similar, yet milder and shorter-lived when compared to PCP. Most patients are treated conservatively and successfully with intravenous hydration and sedation with benzodiazepines.

84 | Antimony

CHEMISTRY

Antimony (Sb) is located in the same group on the periodic table as arsenic (As), and as such, these two elements share many chemical, physical, and toxicologic properties. Because it can react as both metal and nonmetal, antimony is classified as a metalloid. Pure elemental antimony is a lustrous, silver-white, brittle, and hard metal that is rapidly converted to either antimony oxide or antimony trioxide. Thus, for the purposes of this chapter the term *antimony* refers to antimony compounds. Like arsenic, antimony compounds form both organic and inorganic compounds with trivalent and pentavalent oxidation states. Common inorganic trivalent antimony compounds include antimony trioxide (SbO_3), antimony trisulfide (SbS_3), antimony trichloride ($SbCl_3$), antimony potassium tartrate ($C_8H_4K_2O_{12}Sb_2 * 3H_2O$), and stibine ($SbH_3$). Antimony pentasulfide (Sb_2S_5) and pentoxide (Sb_2O_5) are pentavalent inorganic compounds that can act as oxidizing agents. Tartar emetic (antimony potassium tartrate) is an odorless trivalent antimony compound that is a potent emetic with a sweet metallic taste.

TOXICOKINETICS

Absorption

Antimony may be absorbed by inhalation, ingestion, or transcutaneously. Although absorption from the gastrointestinal tract begins immediately upon ingestion, the oral bioavailability of antimony ranges only from 15–50%. This poor gastrointestinal absorption in humans, in addition to the concomitant emesis, necessitates parenteral administration of many antimony-based pharmaceuticals. Pulmonary absorption of many inorganic antimony compounds is very slow and limited by low solubility. In contrast, inhaled trivalent antimony is well absorbed from the lung, distributed to various organs, and subsequently excreted via feces and urine.

Distribution

Distribution depends on the oxidation state of antimony. In animals, more than 95% of trivalent antimony is incorporated into the red blood cells within 2 hours of exposure, whereas in a similar time frame, 90% of pentavalent antimony will still be found in the plasma. Upon intravenous and oral administration, antimony is predominantly distributed among highly vascular organs, including liver, kidneys, thyroid, and adrenals. After inhalation, antimony accumulates predominantly in red blood cells, and to a significantly lesser extent, in the liver and spleen.

Excretion

Trivalent antimony is excreted in the bile after conjugation with glutathione. A significant proportion of excreted antimony undergoes enterohepatic recirculation. The remainder is excreted in urine. The overall elimination is very slow: only 10% of a given dose is cleared in the first 24 hours, 30% is cleared in the first week, and some urinary antimony is still detectable in the urine 100 days after administration. Pentavalent antimony is much more rapidly excreted by kidneys than trivalent antimony (50–60% vs. 10% over the first 24 hours).

PATHOPHYSIOLOGY

Elemental antimony is considered to be more toxic than its salts, but because exposure to the elemental form is relatively uncommon, this fact is of limited clinical relevance. Like other toxic metals, antimony binds to sulfhydryl groups inhibiting a variety of metabolic functions. Trivalent antimony compounds are more toxic than the pentavalent compounds because of their higher affinity for erythrocytes and sulfhydryl groups. Tartar emetic and other antimony salts are also considered local irritants of the gastrointestinal tract. In addition, there is an apparent direct medullary action, particularly after administration of higher doses of antimony.

CLINICAL MANIFESTATIONS

Data on human toxicity of antimony is very limited, and is largely extrapolated from occupationally exposed patients and from the reports of adverse effects during treatment of leishmaniasis with antimony. There are very few case reports of intentional antimony overdoses.

Workers with occupational exposures usually present with subtle clinical symptoms as chronic toxicity develops slowly over time. It is important to recognize that antimony ore contains a small concentration of arsenic as an impurity, making it difficult to distinguish whether effects on workers are caused by coexposure to other xenobiotics or by the antimony. The adverse effects of antiparasitic treatment may be subacute or acute.

Following oral ingestions, acute symptoms mimicking the toxicity of arsenic and other metal salts occur.

Local Irritation

The majority of antimony toxicity results from local irritation. In sufficient concentration, antimony acts as an irritant to the eyes, skin, and mucosa. Chronic exposure can cause conjunctivitis. Irritation of the upper respiratory tract can lead to pharyngitis.

Gastrointestinal

In acute exposures, antimony can rapidly produce nausea, vomiting, abdominal pain, and diarrhea. Some patients may report a metallic taste. In severe overdose, gastrointestinal irritation can progress to hemorrhagic gastritis. Workers chronically exposed to antimony dusts have a high incidence of gastrointestinal ulcers. Pancreatitis is common following treatment with pentavalent antimony compounds.

Cardiovascular

Antimony decreases myocardial contraction and coronary vasomotor tone, producing hypotension and bradycardia. The majority of reported human cardiac effects are related to the changes on electrocardiogram (ECG). Prolongation of the QTc, inversion or flattening of T waves, and ST-segment changes are frequently described. Torsades de pointes is also reported.

Respiratory

Local irritation from antimony trioxide can produce laryngitis, tracheitis, and pneumonitis. Acute lung injury was reported after acute exposure to antimony pentachloride. Antimony oxides are also capable of causing metal fume fever.

Renal

Patients treated with sodium stibogluconate can develop varied manifestations of renal toxicity ranging from renal cells casts, proteinuria, and increased blood urea nitrogen concentration to renal failure. Renal tubular acidosis (RTA) and acute tubular necrosis may occur.

Hematologic

Patients treated with sodium stibogluconate for visceral leishmaniasis occasionally develop anemia and thrombocytopenia. Leukopenia is also frequently observed during therapeutic use of antimony compounds.

Dermatologic

Antimony spots are papules and pustules that develop around sweat and sebaceous glands, and may resemble varicella.

Neurologic

A reversible, peripheral sensory neuropathy is reported in temporal association with antimony treatment.

Reproductive

In animal studies, antimony exposure causes ovarian atrophy, uterine metaplasia, and impaired conception. An association between spontaneous abortion and premature births in women who were occupationally exposed to antimony salts is reported.

STIBINE

Antimony compounds can react with nascent hydrogen forming an extremely toxic gas, stibine (SbH_3), which resembles arsine (AsH_3). Stibine is probably the most toxic antimony compound. It is a colorless gas with very unpleasant smell that rapidly decomposes at temperatures above 302°F (150°C). In addition to GI symptoms that include nausea, vomiting, and abdominal pain, stibine has strong oxidative properties capable of producing massive hemolysis. Similar to arsine, severe stibine exposure may result in hematuria, rhabdomyolysis, and possibly death.

DIAGNOSTIC TESTING

A complete blood count, electrolytes and renal function studies, and a urinalysis should be obtained to help identify volume depletion and renal injury. When there is a known or suspected exposure to stibine, additional studies should include tests for hemolysis, such as determinations of bilirubin and haptoglobin. Blood should also be obtained for a blood type and cross-match, as a transfusion may be required.

An ECG should be obtained to evaluate for QTc prolongation and other changes. Patients with known myocardial disease should have more frequent monitoring of cardiac function and ECG changes.

Antimony concentration in a 24-hour urine collection can be used for assessment of the intensity of exposure to either trivalent or pentavalent antimony. A normal urinary antimony concentration in nonexposed patients is reported to be 0.5–6.2 μg/L. A serum antimony concentration cannot be determined in a timely fashion. However, it is reported that a normal serum concentration of antimony is 0.8–3.0 μg/L.

TREATMENT

Decontamination

Following a significant acute ingestion, the majority of the patients develop vomiting. Induction of emesis is unlikely to offer any additional benefit. In contrast, gastric lavage might be beneficial, especially if performed before the onset of spontaneous emesis. Although it is unknown whether antimony is adsorbed to activated charcoal, based on experience with salts of arsenic, thallium, and mercury, administration of activated charcoal seems reasonable. Additionally, because antimony has a documented enterohepatic circulation, multiple-dose activated charcoal may be of value.

Supportive Care

The mainstay of treatment for antimony poisoning is good supportive care. Volume depletion should be treated with rehydration with isotonic crystalloid solutions. Electrolytes and urine output should be followed closely. A central venous pressure monitor may be required in patients with cardiovascular instability. Antiemetics are indicated both for patient comfort and to facilitate the administration of activated charcoal. Following stibine exposure the hematocrit should be followed closely and blood should be transfused based on standard criteria.

Chelation

Human experience with regard to chelation of antimony is rather limited because of the rarity of patients with serious toxicity. Dimercaprol, succimer, and dimercaptopropane sulfate (DMPS) all improve survival of experimental animals. A single case series documented survival in 3 of 4 patients exposed to tartar emetic following intramuscular dimercaprol at a dose of 200–600 mg/d. Although specific recommendations are difficult to make, it is reasonable to begin therapy with parenteral dimercaprol until it is certain that antimony is no longer present in the gastrointestinal tract, at which time the patient can be switched to oral succimer. Because chelation doses for antimony poisoning are not established, chelators should be administered in doses and regimens that are determined to be safe and effective for other metals.

85 Arsenic

HISTORY/EPIDEMIOLOGY

Arsenic poisoning can be unintentional, suicidal, homicidal, occupational, environmental, or iatrogenic. Contaminated soil, water, and food are the primary sources of arsenic for the general population. Pentavalent arsenic is the most common inorganic form in the environment. In the past 2 decades, consumption of contaminated water has emerged as the primary cause of large-scale outbreaks of chronic arsenic toxicity. The Environmental Protection Agency recently decreased the maximum permissible concentration of arsenic in drinking water to 10 parts per billion (ppb, or 0.01 mg/L), after statistical modeling indicated an increased risk of lung and bladder cancer from water contaminated with arsenic at the formerly acceptable level of 50 ppb.

PHARMACOLOGY

Arsenic trioxide (As_2O_3) is administered therapeutically in conventional doses of 0.15–0.16 mg/kg per day either intravenously or orally. The beneficial effects in acute promyelocytic leukemia occur from initiating cellular apoptosis when arsenic concentrations reach 0.5–2.0 mmol/L. The trivalent arsenic ion binds to mitochondrial membrane sulfhydryl (SH) groups, damaging mitochondrial membranes and collapsing membrane potentials. Low-dose arsenic trioxide treatment (0.08 mg/kg/d) beneficially promotes cell differentiation of acute promyelocytic leukemia (APL) cells when therapeutic arsenic concentrations reach 0.1–2.0 mmol/L. Melarsoprol, the arsenoxide derivative of an organic arsenical, is used to treat the meningoencephalitic stage of West African (Gambian) and East African (Rhodesian) trypanosomiasis. The drug concentrates in trypanosomes via a purine transporter. Its target is trypanothione, the primary reducing agent in trypanosomes. The resulting decrease in trypanothione leads to a loss of reducing capacity with subsequent lysis of the parasite.

PHARMACOKINETICS/TOXICOKINETICS

Estimated human LD_{50} (median lethal dose for 50% of test subjects) doses are reported to be as follows: arsenic trioxide, 1.43 mg/kg; monomethylarsonic acid (MMA), 50 mg/kg; and dimethylarsinic acid (DMA), 500 mg/kg.

Absorption

Inorganic arsenic is tasteless and odorless and is well absorbed by the gastrointestinal, respiratory, intravenous and mucosal routes. Poorly soluble trivalent compounds such as As_2O_3 are less well absorbed than more soluble trivalent and pentavalent compounds. Systemic absorption via the respiratory tract depends on the particulate size, as well as the arsenic compound and its solubility. Large, nonrespirable particles are cleared from the airways by ciliary action and swallowed, allowing GI absorption to occur. Respirable particles lodging in the lungs can be absorbed over days to weeks or remain unabsorbed for years. Dermal penetration of arsenic through intact skin does not pose a risk for acute toxicity.

Pharmacokinetics

Intravenous administration of a single 10-mg dose of As_2O_3 resulted in a maximum plasma concentration (Cp_{max}) of 6.85 μmol/L and a β elimination half-life ($t_{1/2}\beta$) of 12.13 ± 3.31 hours. A study in humans receiving intravenous radioarsenic isotope (^{74}As) showed arsenic clearing from the blood in three phases:

Phase 1 (2–3 hours)—Arsenic is rapidly cleared with a half-life of 1–2 hours; more than 90% may be cleared during this phase.

Phase 2 (3 hours–7 days)—A more gradual decline occurs, with an estimated half-life of 30 hours; by 10 hours postinfusion the arsenic is concentrated in red blood cells (RBCs) by a 3:1 ratio compared to plasma.

Phase 3 (10 or more days)—Clearance continues slowly with an estimated half-life of 300 hours.

Metabolism occurs primarily in the liver but also in the kidneys, testes, and lungs. If the arsenic is pentavalent, approximately 50–70% will first be reduced to trivalent arsenic. Addition of 1 methyl group produces MMA; adding a second methyl group produces DMA.

Urinary elimination of unchanged arsenic and its methylated metabolites occurs via glomerular filtration and tubular secretion; active reabsorption does occur. In the first 4–5 days postingestion, 46–68.9% is eliminated. Approximately 30% is eliminated with a half-life of greater than 1 week, while the remainder is slowly excreted with a half-life of greater than 1 month.

PATHOPHYSIOLOGY

The primary biochemical lesion of As^{3+} is inhibition of the pyruvate dehydrogenase (PDH) complex. This decreases acetyl-coenzyme A (CoA) formation, which decreases citric acid cycle activity, and subsequently impairs adenosine triphosphate (ATP) production. Arsenic also blocks the dihydrolipoamide–lipoamide recycling in the citric acid cycle. In addition, arsenic inhibits thiolase, the catalyst for the final step in fatty acid oxidation, which further decreases ATP. Trivalent arsenic also inhibits glutathione synthetase, glucose-6-phosphate dehydrogenase (required to produce nicotinamide adenine dinucleotide phosphate [NADPH]) and glutathione reductase.

Arsenic blocks cardiac delayed rectifier channels I_{Ks} and I_{Kr}, which are responsible for cardiac repolarization. Toxicity results in ventricular dysrhythmias, including torsades de pointes. Inhibition of glucose transport plus the inhibited gluconeogenesis can lead to glycogen depletion and hypoglycemia.

Toxicity from As^{5+} may occur, in part, from its transformation to As^{3+}. It can also impair oxidative phosphorylation by substituting for inorganic phosphate in the glycolysis. Chronic arsenic exposure is associated with cardiovascular disease, hepatic portal fibrosis, and cancer.

CLINICAL MANIFESTATIONS

Toxic manifestations vary depending on the amount and form of arsenic ingested and the chronicity of ingestion. Larger doses of a potent compound such as arsenic trioxide rapidly produce manifestations of acute toxicity, whereas chronic ingestion of substantially lower amounts of arsenic in groundwater slowly result in a different clinical picture. Manifestations of subacute toxicity can develop in patients who survive acute poisoning, as well as in patients who are slowly poisoned environmentally.

Acute Toxicity

Gastrointestinal signs and symptoms of nausea, vomiting, abdominal pain, and diarrhea are the earliest manifestations of acute poisoning by the oral route. They occur minutes to several hours following ingestion. The diarrhea has been compared to that seen with cholera and may resemble "rice water." Severe multisystem illness can result both from volume depletion and direct toxic effects. Cardiovascular signs ranging from sinus tachycardia and orthostatic hypotension to shock can develop. A prolonged QTc can be followed by ventricular dysrhythmias. Acute encephalopathy can develop and progress over several days, with delirium, coma, and seizures attributed to cerebral edema and microhemorrhages. Acute lung injury, acute respiratory distress syndrome (ARDS), and respiratory failure, hepatitis, hemolytic anemia, acute renal failure, rhabdomyolysis, and death can occur. Acute renal failure may be secondary to ischemia caused by hypotension, tubular deposition of myoglobin or hemoglobin, renal cortical necrosis, and direct renal tubular toxicity.

Subacute Toxicity

In the days and weeks following an acute exposure, prolonged or additional signs and symptoms in the nervous, gastrointestinal, hematologic, dermatologic, pulmonary, and cardiovascular systems can occur. Encephalopathic symptoms of headache, confusion, decreased memory, personality change, irritability, hallucinations, delirium, and seizures may develop and persist. Sixth cranial nerve palsy and bilateral sensorineural hearing loss are reported. Peripheral neuropathy typically develops 1–3 weeks after acute poisoning, although it can occur earlier. Dermatologic lesions can include patchy alopecia, oral herpetiform lesions, a diffuse pruritic macular rash, and a brawny nonpruritic desquamation. Mees lines, transverse striate leuconychia of the nails, are 1–2 mm wide and rarely occur in arsenic poisoning. Other possible toxic manifestations of subacute inorganic arsenic toxicity include nephropathy, fatigue, anorexia with weight loss, torsades de pointes, and persistence of gastrointestinal symptoms.

Chronic Toxicity

Chronic low-level exposure to inorganic arsenicals typically occurs from occupational or environmental sources. Gastrointestinal symptoms of nausea, vomiting, and diarrhea are less likely than with acute toxicity, but can occur. Malignant and nonmalignant skin changes, hypertension, diabetes mellitus, peripheral vascular disease, and several internal malignancies are associated with consumption of arsenic in drinking. The skin is very susceptible to the toxic effects of arsenic. Multiple lesions are reported, including hyperpigmentation, hyperkeratosis, squamous and basal cell carcinomas, and Bowen disease. Population studies show an increased prevalence of diabetes mellitus, restrictive lung disease, and vascular disease. Blackfoot disease, an obliterative arterial disease of the lower extremities occurring in Taiwan, has been linked with chronic arsenic exposure. Encephalopathy and peripheral neuropathy are the neurologic manifestations most commonly reported.

DIAGNOSTIC TESTING

Timing of testing for arsenic must be correlated with the clinical course of the patient, whether the poisoning is acute, subacute, chronic, or remote with re-

sidual clinical effects. Confounding factors, such as food-derived organic arsenicals or accumulated arsenic (DMA and arsenobetaine) in patients with chronic renal failure, must be considered to properly interpret laboratory measurements. In an emergency, a spot urine may be sent prior to beginning chelation therapy. A markedly elevated arsenic concentration verifies the diagnosis in a patient with characteristic history and clinical findings, whereas a low concentration does not exclude arsenic toxicity. In acutely symptomatic patients, initial spot urine arsenic concentrations ranged from 192–198,450 μg/L. Because urinary excretion of arsenic is intermittent, definitive diagnosis hinges upon finding a 24-hour urinary concentration ≥50 μg/L or 100 μg/g creatinine.

When interpreting slightly elevated urinary arsenic concentrations, laboratory findings must also be correlated with the history and clinical findings, as seafood ingestion has been reported to transiently elevate urinary arsenic excretion up to 1700 μg/L. When seafood arsenic is a consideration, speciation of arsenic can be accomplished. If arsenic speciation cannot be done, the patient can be retested after a 1 week abstinence from fish, shellfish, and algae food products.

Diagnostic evaluation of chronic toxicity should include laboratory parameters that may become abnormal within days to weeks following an acute exposure. Tests should include a complete blood count (CBC), liver enzymes, and renal function tests, urinalysis as well as 24-hour urinary arsenic determinations. Complete blood count findings can include a normocytic, normochromic, or megaloblastic anemia, an initial leukocytosis followed by development of leukopenia with neutrophils depressed more than lymphocytes, a relative eosinophilia, thrombocytopenia, and a rapidly declining hemoglobin indicative of hemolysis or a gastrointestinal hemorrhage. Basophilic stippling of RBCs can also be seen. Elevated serum creatinine, aminotransferases, and bilirubin as well as depressed haptoglobin concentrations may develop. Urinalysis may reveal proteinuria, hematuria, and pyuria. Urinary arsenic excretion in subacute and chronic cases varies inversely with the postexposure time period, but low-concentration excretion may continue for months after exposure.

Abdominal radiographs may demonstrate radiopaque material in the gastrointestinal tract soon after ingestion. Because the sensitivity and specificity of abdominal radiographs are unknown, a negative radiograph does not exclude arsenic ingestion. Electrocardiographic changes reported include QRS widening, QTc prolongation, ST-segment depression, T-wave flattening, ventricular premature contractions, nonsustained monomorphic ventricular tachycardia, and torsades de pointes. Nerve conduction studies can confirm or diagnose clinical or subclinical axonopathy.

MANAGEMENT

Acute arsenical toxicity is life-threatening and mandates aggressive treatment. Advanced life-support monitoring and therapies should be initiated when necessary, with a few caveats. Careful attention to fluid balance is important, because cerebral and pulmonary edema may be present. Medications that prolong the QTc, such as the classes IA, IC, and III antidysrhythmics, should be avoided. Potassium, magnesium, and calcium concentrations should be maintained within normal range to avoid exacerbating a prolonged QTc. Glucose concentrations and glycogen stores should be maintained.

Although arsenic is poorly adsorbed to activated charcoal in vitro, clinically significant adsorption may occur. If radiopaque material is present in the gastrointestinal tract, whole-bowel irrigation can also be administered. Arsenic can be readily removed from skin with soap, water, and vigorous scrubbing.

The initiation of chelation therapy depends on the clinical condition of the patient as well as the arsenic concentration. A severely ill patient with known or suspected acute poisoning should be chelated immediately, even before laboratory confirmation is received. Cases of subacute and chronic toxicity can await rapid laboratory confirmation prior to beginning chelation, unless the clinical condition deteriorates. Dimercaprol (British anti-Lewisite, or BAL) and meso-2,3-dimercaptosuccinic acid (succimer) are the two chelators available in the United States. Dosing regimens and adverse effects are discussed in the Antidotes in Brief sections. BAL remains the initial chelating drug for acute arsenical toxicity. It is administered parenterally and thus is not affected by the patient's gastrointestinal motility. However, because of its narrow therapeutic index, most patients should be switched to succimer once their gastrointestinal tract has been decontaminated and they are hemodynamically stable. D-Penicillamine has not demonstrated efficacy in chelating or reversing the biochemical toxicity of arsenic and should not be used.

Hemodialysis

Hemodialysis removes negligible amounts of arsenic, with or without concomitant BAL therapy, and is not indicated in patients with normal renal function. In patients with renal failure, hemodialysis clearance rates have ranged from 76–87.5 mL/min. A 4-hour dialysis session is only reported to remove on the order of 3–5 mg of arsenic, which is inconsequential when compared to normal renal elimination.

Dimercaprol (British Anti-Lewisite or BAL)

PRINCIPLES OF CHELATION

Soft metals such as Hg^{2+}, Au^{+}, Cu^{+}, and Ag^{+} have large atomic radii with a large number of electrons in their outer shell. Accordingly, they form the most stable complexes with sulfur donors and are therefore referred to as sulfur seekers. The chelator or ligand, in this case a sulfur-containing compound such as dimercaprol (BAL), forms a coordinate bond with the metal by donating a pair of free electrons. BAL has two adjacent sulfur groups, thus the term *dithiol*; the presence of these two sulfur groups permits the formation of a ring structure with the metal, thereby enhancing chelator stability through a soft ligand bond. Hard metals, such as Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, and Al^{3+}, are referred to as oxygen seekers and form the best complexes with hard ligands containing a carboxyl (COO^{-}) group such as edetate calcium disodium ($CaNa_2EDTA$). Borderline metals, such as Pb^{2+}, Cd^{2+}, Cu^{2+}, As^{3+}, and Zn^{2+}, prefer nitrogen-donating ligands, but will also react with both hard and soft ligands.

The most useful chelators have relatively low intrinsic toxicity, form stable complexes with the chelated metals, have tissue distribution characteristics similar to the metal to be chelated and when administered effect a favorable clinical outcome. Other desirable aspects of the metal–chelator complex are elimination from the body intact, and the lack of redistribution to the brain or other critical organs. Unfortunately, there is no currently available chelator with all of these attributes. Thus much of our current practice relies on opinion and historical precedence and many pharmacokinetics and toxicokinetics questions remain unanswered.

CHEMISTRY

BAL is an oily liquid with only 6% weight/volume water solubility, 5% weight/volume peanut oil solubility, and a disagreeable odor. Aqueous solutions are easily oxidized and therefore unstable. Peanut oil stabilizes BAL and benzyl benzoate (in the ratio of 1 part BAL to 2 parts of benzyl benzoate) renders the BAL miscible with peanut oil.

PHARMACOKINETICS

Following IM administration, blood concentrations of BAL peak in about 30 minutes, distribution occurs quickly, and blood concentrations begin to fall within 2 hours. Urinary excretion of BAL metabolites accounts for nearly 45% of the dose within 6 hours and 81% of the dose within 24 hours. BAL is concentrated in the kidney, liver, and small intestine. BAL can also be found in the feces, strongly implying that enterohepatic circulation exists. Hemodialysis may be useful in removing the BAL–metal chelate in cases of renal failure.

USE FOR ARSENIC POISONING

Animal Studies

In a rodent model, low concentrations of topical BAL were very effective in preventing Lewisite-induced toxicity and in reversing toxicity when adminis-

tered within 1 hour of skin exposure. In rabbits, ocular application of BAL proved effective in preventing eye destruction if applied within 20 minutes of exposure. The effectiveness of both parenteral single-dose and multiple-dose BAL against Lewisite and other arsenicals was studied in rabbits. When begun within 2 hours of Lewisite exposure, BAL injections of 4 mg/kg every 4 hours led to a 50% survival of exposed rabbits. More recent animal studies demonstrate that although dimercaprol increases the LD_{50} (median lethal dose for 50% of test subjects) of sodium arsenite, the therapeutic index of BAL is low and arsenic redistribution to the brain occurs. In these same animal models, succimer and the investigational agent 2,3-dimercaptopropane sulfonate (DMPS) also increased the LD_{50}, but with a better therapeutic index and without causing redistribution to the brain.

Human Studies

Experiments in human volunteers given minute amounts of arsenic demonstrated that BAL increased urinary arsenic concentration by approximately 40%, with maximum excretion occurring 2–4 hours after BAL administration. Intramuscular BAL produced both subjective and objective improvement, limited the duration of the arsenical dermatitis, and increased urinary arsenic elimination. In 227 patients with inorganic arsenic poisoning, maximal efficacy and minimal toxicity were achieved when 3 mg/kg of BAL was administered intramuscularly every 4 hours for 48 hours and then twice daily for 7–10 days. This regimen resulted in complete recovery in 6 of 7 patients with severe arsenic-induced encephalopathy. Of 33 patients with severe arsenic-induced encephalopathy in another study, 18 of 24 (75%) treated within 6 hours survived, versus only 4 of 9 (44%) treated after a delay of at least 72 hours.

USE FOR MERCURY POISONING

The clinical efficacy of BAL in treating inorganic mercury poisoning is substantiated in patients who ingested mercury bichloride. Thirty-eight patients ingesting more than 1 g of mercuric chloride who were treated with BAL within 4 hours of exposure were compared to historical controls. There were no deaths in the 38 patients treated with BAL as compared to 27 deaths in the 86 untreated patients. BAL is particularly useful for patients who have ingested a mercuric salt, as the associated gastrointestinal toxicity of the mercuric salt limits the potential of an orally administered antidote such as succimer.

We do not recommend BAL therapy when patients are exposed to short-chain organic mercury compounds because it may increase brain concentrations of methyl mercury and other agents may have greater usefulness.

USE FOR LEAD POISONING

BAL may be used in combination with $CaNa_2EDTA$ to treat patients with severe lead poisoning. In all other cases, succimer has become the chelator of choice. When administering BAL in patients with lead encephalopathy, it is essential to administer the BAL first, followed 4 hours later by $CaNa_2EDTA$ concomitantly with the second dose of BAL. This regimen prevents the $CaNa_2EDTA$ from redistributing lead into the brain. Once the mobilization of lead has begun, it is important to provide uninterrupted therapy to prevent redistribution of lead to the brain.

ADVERSE EFFECTS AND SAFETY ISSUES

The toxicity of BAL is dose-dependent and affected by urinary pH. An acidic urine allows dissociation of the BAL–metal chelate. Less than 1% of 700 intramuscular injections result in minor reactions, such as pain, among patients who receive 2.5 mg/kg of BAL every 4–6 hours for 4 doses. When doses of 4 mg/kg and 5 mg/kg are given, the incidence of adverse effects rises to 14% and 65%, respectively. At these higher doses, reported symptoms include, in decreasing order of frequency, nausea, vomiting; headache; burning sensation of lips, mouth, throat, and eyes; lacrimation; rhinorrhea; salivation; muscle aches; burning and tingling of extremities; tooth pain; diaphoresis; chest pain; anxiety; and agitation. Elevations in systolic and diastolic blood pressure and tachycardia commonly occurred and correlated with increasing doses. Thirty percent of children given BAL may develop a fever that can persist throughout the therapeutic period.

Because dissociation of the BAL–metal chelate will occur in an acid urine, the urine of patients receiving BAL should be alkalinized with hypertonic sodium bicarbonate to a pH of 7.5–8.0 to prevent renal liberation of the metal. BAL should be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as it may cause hemolysis. Because BAL is formulated in peanut oil, the patient should be questioned regarding any known peanut allergy. Unintentional IV infusion of BAL could theoretically produce fat embolism, lipoid pneumonia, chylothorax, and associated hypoxia.

DOSING

The dose of BAL for lead encephalopathy is 75 mg/m^2 IM every 4 hours for 5 days. As noted earlier, the first dose of dimercaprol should precede the first dose of $CaNa_2EDTA$ by 4 hours.

The dose of BAL for severe inorganic arsenic poisoning has not been established. One regimen suggests the use of 3 mg/kg IM every 4 hours for 48 hours and then twice daily for 7–10 days. Another regimen uses 3–5 mg/kg IM every 4–6 hours on the first day and then tapers the dose and frequency, depending on the patient's symptomatology. A third regimen reduces the number of injections by day 2 and terminates therapy within 5–7 days.

The dose of BAL for patients exposed to inorganic mercury salts is 5 mg/kg IM initially, followed by 2.5 mg/kg every 8–12 hours for 1 day, followed by 2.5 mg/kg every 12–24 hours until the patient appears clinically improved, up to a total of 10 days.

AVAILABILITY

BAL is available in 3-mL ampules containing 100 mg/mL of BAL, 200 mg/mL of benzyl benzoate, and 700 mg/mL of peanut oil. This drug should only be administered by deep IM injection.

86 Bismuth

HISTORY AND EPIDEMIOLOGY

Nearly 300 years ago, bismuth was recognized as medicinally valuable. It was included in topical salves and oral preparations for various gastrointestinal disorders. Renal toxicity was described as early as 1802. In the early 20th century, cases of renal failure were reported in children administered intramuscular bismuth salts for the treatment of gingivostomatitis.

Syphilis was previously treated with intramuscular bismuth. A rash known as "erythema of the 9th day" occasionally occurred. This consisted of a diffuse macular rash of the trunk and extremities that resolved without intervention. More recently, epidemics of bismuth-induced encephalopathy occurred, particularly among patients with ileostomies or colostomies.

TOXICOKINETICS

Bismuth is present in nature in both trivalent and pentavalent forms. The trivalent form of bismuth is employed for all medicinal uses, as the bismuthyl (BiO) moiety. Most of orally administered bismuth remains in the gastrointestinal (GI) tract, being excreted in the feces, and only 0.2% is systemically absorbed. Absorption of some bismuth preparations, such as colloidal bismuth subcitrate, may increase as gastric pH increases. The distribution and elimination of orally administered bismuth follows a complex, multicompartmental model. The volume of distribution in humans is unknown.

Once in the circulation, bismuth binds to α_2-macroglobulin, IgM, β-lipoprotein, and haptoglobin. Bismuth rapidly enters liver, kidney, lungs, and bone. Bismuth can cross the placenta and enter the amniotic fluid and fetal circulation. It also readily crosses the blood–brain barrier. Ninety percent of absorbed bismuth is eliminated through the kidneys, where it induces the production of its own metal-binding protein.

Three different half-lives describe the pharmacokinetics of orally administered bismuth: the distribution half-life is approximately 1–4 hours; the plasma half-life lasts 5–11 days; and the half-life of urinary excretion lasts between 21 and 72 days, with urinary bismuth detected as long as 5 months after the last oral dose.

PATHOPHYSIOLOGY

The effect of different bismuth salts can be categorized into four groups based upon solubility and gastrointestinal absorption (Table 86–1).

The mechanism of bismuth-induced encephalopathy is thought to be related to neuronal sulfhydryl binding. The factors predisposing some individuals to encephalopathy from group II bismuth salts, however, are not well defined. Age, gender, and duration of therapeutic use do not predict the likelihood of developing encephalopathy.

CLINICAL MANIFESTATIONS

Acute

Acutely, massive overdoses result in abdominal pain and oliguria or anuria. Acute renal failure can occur and is not limited to exposure to the water-solu-

TABLE 86–1. The Characteristics of Bismuth Salts

Group	Chemistry	Primary Toxicity	Examples
I	Insoluble in water Inorganic	Minimal	Bismuth subnitrate Bismuth subcarbonate
II	Lipid soluble Organic	Neurologic	Bismuth subsalicylate Bismuth subgallate
III	Water soluble Organic	Renal	Bismuth triglycollamate
IV	Hydrolyzable Water soluble Organic	Minimal	Bicitropeptide

ble bismuth salts (group III). Bismuth causes degeneration of the proximal renal tubule, similar to other heavy metals.

Chronic

The most common finding associated with repeated doses of oral bismuth is a diffuse, progressive encephalopathy. Patients exhibit neurobehavioral changes, such as apathy and irritability followed by difficulty concentrating, diminished short-term memory, and, occasionally, visual hallucinations. A movement disorder characterized by muscle twitching, myoclonus, ataxia, and tremors may ensue. Weakness and, rarely, seizures may advance to immobility. With continued bismuth administration these patients can develop coma and die.

Fractures may be caused by severe neuromuscular manifestations such as myoclonus. Like several other heavy metals, bismuth can cause a generalized pigmentation of skin. Deposition of bismuth sulfide into the mucosa causes a blue-black discoloration of gums. Formation of the same compound in the gastrointestinal tract causes blackening of the stool.

DIAGNOSIS

The diagnosis of bismuth-induced encephalopathy is based on a history of exposure coupled with diffuse neuropsychiatric and motor findings. Other causes of encephalopathy should be entertained and excluded. An abdominal radiograph may demonstrate radiopacities of bismuth in the intestines. Stool will be black, but will test negative for occult blood.

Blood bismuth concentrations confirm exposure, but absolute concentrations correlate poorly with morbidity. Although patients with encephalopathy typically have a blood concentration >100 ng/mL (with the majority between 100 and 1000 ng/mL), encephalopathy with blood concentrations below 100 ng/mL is reported.

The electroencephalographic (EEG) findings of patients with bismuth encephalopathy generally demonstrate nonspecific slow wave changes. In encephalopathic patients with blood concentrations >2000 ng/mL diagnostic imaging, such as computed tomography, may demonstrate a diffuse cortical hyperdensity of the gray matter. These findings tend to resolve with recovery. Magnetic resonance imaging was normal in one encephalopathic patient.

CHELATION

Chelation therapy with British anti-Lewisite (BAL) is beneficial in experimental models, reportedly beneficial in humans, and often recommended, al-

though clear evidence of efficacy is lacking. BAL undergoes biliary elimination, offering a major advantage over other chelators in patients who may develop renal insufficiency. In human volunteers following colloidal bismuth subcitrate exposure, succimer and dimercaptopropane sulfonate (DMPS) increased urinary elimination of bismuth by 50-fold.

TREATMENT

Typically, supportive care results in a complete recovery. Gastrointestinal decontamination with activated charcoal and polyethylene glycol solution seems reasonable, especially in patients with severe encephalopathy, although evidence is lacking. Chelating agents should only be considered in patients with neurotoxicity, although withdrawal of the source of bismuth usually results in complete reversal of symptoms within days to weeks, even in severely ill patients. The precise timing, dosage, indications, and choice of chelator are unknown; however, chelation with succimer is well tolerated. BAL, which has more side effects, can be considered in encephalopathic patients with renal failure in whom no neurologic improvement is noted within 48 hours of bismuth withdrawal and treatment with whole-bowel irrigation.

SPECIAL CONSIDERATIONS

In the United States, where bismuth subsalicylate is the most common oral bismuth-containing compound, up to 90% of the salicylate is absorbed. Salicylate toxicity has been reported and salicylate concentrations should be performed in both acute and chronic exposures. Methemoglobinemia from subnitrate salt of bismuth is rarely described.

87 Cadmium

HISTORY AND EPIDEMIOLOGY

Cadmium is principally used as a reagent in electroplating and in the production of nickel-cadmium batteries. Cadmium is used as a pigment, as part of the phosphorescent system in black-and-white televisions, and as a neutron absorber in nuclear reactors. Cadmium toxicity usually results from environmental, occupational, or hobby exposures.

Environmental Exposure

Environmental exposure to cadmium generally occurs through the consumption of foods grown in cadmium-contaminated areas. Because cadmium is fairly common as an impurity in ores, areas where mining or refining of ores takes place are at highest risk for contamination. In the 1950s, a Japanese mine discharged large amounts of cadmium into the environment, contaminating the rice that was a staple of the local food supply. An epidemic of painful osteomalacia followed, affecting hundreds of people, with postmenopausal multiparous women being most affected. The afflicted were prone to develop pathologic fractures, and were reported to call out "itai-itai" (translated literally as "ouch-ouch") as they walked, because of the severity of their pain.

Occupational and Hobby Exposure

Significant cadmium toxicity invariably results from metalworking in a closed space with inadequate ventilation and/or improper respiratory precautions. Welders, solderers, and jewelry workers, as well as hobbyists who use cadmium-containing alloys, are at risk of developing acute cadmium toxicity through inhalation of cadmium oxide fumes.

TOXICOKINETICS

There is no known biologic role for cadmium. The bioavailability of elemental cadmium is unknown. Cadmium salts are poorly orally bioavailable (5–20%). However, inhaled cadmium fumes (cadmium oxide) are readily bioavailable (up to 90%). Because the only data on cadmium toxicokinetics come from work with cadmium salts and oxides, "cadmium" in the following discussion refers to these species unless otherwise noted. After exposure, cadmium is taken up into the bloodstream, where it is bound to α_2-macroglobulin and albumin. It is then quickly and preferentially redistributed to the liver and kidney.

After it is incorporated in the liver and kidney, cadmium is complexed with metallothionein, which binds and sequesters cadmium. Slowly, hepatic stores of the cadmium–metallothionein complex (Cd-MT) are released. Circulating Cd-MT is then filtered by the glomerulus. A significant amount of cadmium is then reabsorbed and concentrated in proximal tubular cells. The slow release of cadmium from metallothionein-complexed hepatic stores accounts for its very long biologic half-life of 10 or more years.

PATHOPHYSIOLOGY

Unbound cadmium mediates cellular damage; the metallothionein complex is protective and functions as a natural chelating agent with a strong affinity for cadmium. Cadmium binds to sulfhydryl groups, denaturing proteins, and/or inactivating enzymes. The mitochondria are severely effected by this process, which may result in an increased susceptibility to oxidative stress. Cadmium also interferes with cell–cell adhesion and with calcium transport mechanisms, which might lead to intracellular hypercalcemia and, ultimately, apoptosis.

CLINICAL MANIFESTATIONS

Acute Poisoning

Pulmonary/Cadmium Fumes

Cadmium pneumonitis results from inhalation of cadmium oxide fumes. The acute phase of cadmium pneumonitis may mimic metal fume fever, but these two entities are distinctly different. Whereas metal fume fever is benign and self-limited, acute cadmium pneumonitis can progress to hypoxia, respiratory insufficiency, and death. Within 6–12 hours of closed space exposure, patients typically develop constitutional symptoms, such as fever and chills, as well as a cough and respiratory distress. On initial presentation, these patients may not appear significantly ill and may have a normal physical examination, oxygenation status, and chest radiograph. Subsequently, as the pneumonitis progresses to acute lung injury (ALI), crackles and rhonchi develop, oxygenation becomes impaired, and the chest radiograph develops a pattern consistent with alveolar filling. Despite aggressive supportive care, death may occur, usually within 3–5 days. Patients who survive acute cadmium pneumonitis may develop chronic pulmonary ailments, including diffusion abnormalities, restrictive lung disease, and pulmonary fibrosis.

Oral/Cadmium Salts

Although most acute cadmium exposures are inhalational, acute oral exposures also occur. These cases are characterized by the rapid onset of hemorrhagic gastroenteritis followed by hypotension and multisystem organ failure. Facial and pharyngeal edema is also reported.

Chronic Poisoning

Nephrotoxicity

The most common finding in chronic cadmium poisoning is proteinuria. Renal damage caused by cadmium develops over years. Proteinuria is the most common clinical finding, and correlates with proximal tubular dysfunction, which manifests as urinary loss of low-molecular-weight proteins such as α_2-microglobulin and retinol binding protein. There is a dose–response relationship between total body cadmium burden and renal dysfunction. Cadmium also produces hypercalcuria and occupational cadmium exposure is associated with nephrolithiasis.

Pulmonary Toxicity

Large studies of workers chronically exposed to cadmium fail to demonstrate consistent effects on chronic lung function. Cadmium is associated with pulmonary cancer.

Musculoskeletal Toxicity Bone

Cadmium-induced osteomalacia is a result of abnormalities in calcium and phosphate homeostasis, which also results from renal proximal tubular dysfunction. Osteomalacia, one of the most prominent features of the Itai-Itai epidemic, is a condition in which inadequate mineralization of mature bone predisposes to pathologic fractures. Although mentioned in case reports, osteomalacia is generally not a prominent feature following occupational exposure to cadmium.

Hepatotoxicity

Although the liver stores as much cadmium as any other organ, hepatotoxicity is not a prominent feature of human cadmium exposure, probably because hepatic cadmium is usually complexed to metallothionein.

Neurologic Toxicity

Cadmium exposure is linked to olfactory disturbances, impaired higher cortical function, and Parkinson syndrome.

Cancer

Cadmium induces tumors in multiple animal organs, an effect that is exacerbated by zinc deficiency. In humans, cadmium exposure is associated with lung cancer. The strength of this association was recently questioned, particularly because most studies have methodologic problems such as coexposure to arsenic, a known pulmonary carcinogen.

DIAGNOSTIC TESTING

Other than to confirm exposure, cadmium concentrations have limited usefulness in the management of the acutely exposed patient. Diagnosis and treatment are based on the patient's history, physical examination, and symptoms. In a patient exposed to cadmium oxide fumes, ancillary tests, such as arterial blood gas analysis and chest radiography, are more useful than actual cadmium concentrations.

In patients chronically exposed to cadmium, urinary concentrations, which reflect the slow, steady-state turnover and release of metallothionein-bound cadmium from the liver, are a better reflection of the total-body cadmium burden than are blood concentrations. Workers at high risk for cadmium toxicity should undergo a regular urinalysis for proteinuria. For asymptomatic workers without proteinuria, 15 μg Cd/g urinary creatinine is considered acceptable, although renal dysfunction has occurred infrequently at concentrations as low as 5 μg Cd/g urinary creatinine. This concentration is significantly higher than that of the general US population, 95% of whom have concentrations that are less than 2 μg Cd/g urinary creatinine.

MANAGEMENT

Acute Exposure

Oral Exposure/Cadmium Salts

After the status of the patient's airway, breathing, and circulation have been addressed, attention can be given to gastrointestinal decontamination. Although large oral exposures to soluble cadmium salts are rare, they frequently prove fatal.

Five grams is the lowest reported human lethal dose. Thus, if a significant exposure occurs and emesis has not occurred, gastric lavage is appropriate. In this situation, a small nasogastric tube should suffice, as inorganic cadmium salts are powders, not pills. There are no specific data regarding the use of activated charcoal for acute oral cadmium toxicity; however, activated charcoal is a relatively benign intervention and is clearly indicated in the treatment of some metals.

Given the relative lack of experience with acute oral cadmium poisoning, all patients with known exposures and/or abnormal findings consistent with cadmium toxicity or exposure should be admitted to the hospital for supportive care, monitoring of renal and hepatic function, and possibly for evaluation of the gastrointestinal tract for injury.

The benefits of chelation in acute cadmium exposure are unproven. Multiple chelating agents have been tried, all in animal models, with inconsistent results. Succimer decreases the gastrointestinal absorption of cadmium and improves survival without increasing cadmium burdens in target organs. The succimer should be given as soon as possible after the ingestion, as the effectiveness of chelating agents decreases dramatically over time in experimental models of cadmium poisoning. Doses that are well tolerated (10 mg/kg 3 times per day) are appropriate. Most other chelating agents have been found to be ineffective or even detrimental, including 2,3-dimercaptopropanol (British anti-Lewisite [BAL]), penicillamine, and ethylenediaminetetraacetic acid (EDTA).

Pulmonary/Cadmium Fumes

The patient who is ill after exposure to cadmium fumes (generally cadmium oxide) invariably presents with respiratory complaints and possibly with constitutional symptoms. The airway should be assessed and appropriate oxygenation assured, although hypoxia may not be a problem acutely. Steroids are used in most reported cases, but there are no studies to support their efficacy. Chelation has no role in patients with single acute exposures to cadmium fumes, as these patients do not appear to develop extrapulmonary injury.

All patients with acute inhalational exposures to cadmium should be admitted to the hospital for observation and supportive care given until respiratory symptoms have resolved. Long-term followup should be arranged with a pulmonologist to assess the possibility of chronic lung injury, even in instances of single exposures.

Chronic Exposure

Patients chronically exposed to cadmium frequently come to attention during routine screening, as those who work with cadmium are under close medical surveillance. These patients may have developed proteinuria or, less commonly, chronic pulmonary complaints.

Management is challenging. Cessation of cadmium exposure is the first intervention. However, as mentioned earlier, chronic cadmium-induced renal and pulmonary changes are largely irreversible.

Chelation for chronic cadmium toxicity is not currently recommended. There is no evidence that chelation of chronically poisoned animals improves long-term outcomes. Furthermore, in a chronically exposed patient, the majority of cadmium is bound to intracellular metallothionein, which greatly reduces its toxicity. Any attempt to remove cadmium from these deposits risks redistributing cadmium to other organs, possibly exacerbating toxicity, as is known to occur with BAL therapy.

88 Chromium

HISTORY AND EPIDEMIOLOGY

Chromium (Cr) is a naturally occurring element that may be found in oxidation states of –2 to +6, but primarily in the trivalent (Cr^{3+}) and hexavalent (Cr^{6+}) forms. It occurs only in combination with other elements, primarily existing as halides, oxides, or sulfides. Elemental chromium (Cr^0) does not exist naturally.

Elemental chromium is a blue-white metal that is hard, brittle, and can be added to steel to form stainless steel. One of the most important uses of chrome plating is to apply a hard, smooth surface to machine parts, such as crankshafts, printing rollers, ball bearings, and cutting tools.

The carcinogenic potential of hexavalent chromium was first recognized as a result of nasal tumors in Scottish chrome pigment workers in the late 1800s. In the 1930s, the pulmonary carcinogenicity of chromium was described in German chromate workers.

CHEMICAL PRINCIPLES

Chromium is an essential element involved in glucose metabolism. Chromium deficiency may play a role in the development of diabetes mellitus and of atherosclerosis. The chemical properties and health risks of chromium depend mostly on its oxidative state and on the solubility of the chromium compound. The Cr^{6+} and Cr^{3+} oxidation states have very different properties. Reduction of Cr^{6+} to Cr^{3+} occurs in vivo by abstraction of electrons from cellular constituents such as proteins, lipids, DNA, and RNA, and plasma transferrin.

Environmental Exposure

Processing of chromium ores releases Cr^{3+} into the environment. The most significant environmental sources of Cr^{6+} are chromate production, ferrochrome pigment manufacturing, chrome plating, and some types of welding. People may be exposed to chromium via drinking water, food and food supplements (eg, chromium picolinate), joint arthroplasty, and cigarettes. CCA (copper, chromate, and arsenate)-treated lumber was voluntarily removed from the consumer market in December 2003, because of health concerns with regard to the arsenic and chromium constituents.

PHARMACOLOGY AND PHYSIOLOGY

Because they possess significantly different properties, trivalent and hexavalent chromium must be evaluated separately.

Absorption

After oral administration, absorption of Cr^{3+} salts is limited. Approximately 98% of the compound is recovered in the feces, just 0.1% is excreted in the bile, and 0.5–2.0% is excreted in the urine. Partly as a result of the structural similarity between hexavalent chromium compounds and phosphate and sulfate, Cr^{6+} is modestly absorbed after ingestion. Like trivalent compounds, hexavalent chromium compounds are generally not well absorbed after der-

mal exposure. In contrast, however, inhalation of Cr^{6+} is the most consequential route of exposure. Animal studies suggest that roughly 50–85% of small (<5 μm) inhaled Cr^{6+} potassium dichromate particles are absorbed.

Distribution

Because most of the Cr^{6+} is rapidly reduced upon absorption, Cr^{3+} accounts for virtually the entire body burden of chromium. Trivalent chromium accumulates to the greatest extent in the kidneys, bone marrow, lungs, lymph nodes, liver, spleen, and testes. The kidneys and liver account for approximately 50% of the total body burden.

Elimination

Urinary excretion of trivalent chromium occurs rapidly. Roughly 80% of parenterally administered Cr^{6+} is excreted as Cr^{3+} in the urine and 2–20% in the feces. The urinary excretion half-life of Cr^{6+} ranges from 15–41 hours. As Cr^{6+} undergoes reduction to Cr^{3+} following uptake by red blood cells, there is the creation of an apparent slow compartment, with the elimination half-life dependent on the life span of erythrocytes.

PATHOPHYSIOLOGY

Trivalent Chromium

Chromium picolinate is a popular Cr^{3+} dietary supplement that is often ingested in large daily doses. There is a dearth of rigorous evidence concerning the efficacy or safety of chromium picolinate. However, it appears that organ deposition of Cr^{3+} does occur. Animal work and epidemiologic studies of workers exposed to Cr^{3+} compounds have failed to demonstrate a statistically significant increased incidence of cancer. There is no strong evidence of any significant end-organ toxicity as a consequence of exposure to Cr^{3+}, perhaps because Cr^{3+} is so poorly absorbed.

Hexavalent Chromium

Hexavalent chromium is a powerful oxidizing agent that has corrosive and irritant effects. However, the greatest toxicity from Cr^{6+} lies in its ability to produce oxidative DNA damage. Although the exact mechanisms whereby Cr^{6+} is genotoxic are unknown, transient toxic chromium intermediates such as Cr^{4+} and Cr^{5+} formed during the intracellular reduction of Cr^{6+} to Cr^{3+} are probably responsible.

CLINICAL MANIFESTATIONS

The clinical manifestations of chromium poisoning depend on the valence of the element, the source and route of exposure, and the duration of exposure. The clinical manifestations of chromium exposure are best divided into acute and chronic (low-level exposure) effects.

Manifestations of acute, massive Cr^{6+} ingestions are similar to other corrosive metal ingestions. Gastrointestinal hemorrhage with or without bowel perforation may occur acutely and may lead to hepatic and pancreatic necrosis. Because of the strong oxidative properties of hexavalent chromium, intravascular hemolysis with disseminated intravascular coagulation may also develop. Renal effects include acute tubular necrosis leading to renal failure.

Metabolic abnormalities after acute, massive, exposure include lactic acidosis, hyperkalemia, and uremia. Although Cr^{6+} is generally not well absorbed after dermal exposure, it is a corrosive that causes inflammation and ulceration. Dermal chromic acid (H_2CrO_4) burns may lead to severe systemic toxicity with as little as 10% body surface area involvement.

The respiratory tract is the organ most affected after chromium exposure. When inhaled, Cr^{6+} is a respiratory tract irritant that causes inflammation and, with continued exposure, ulceration (including nasal septal perforation). Furthermore, the sensitizing effects of Cr^{6+} may lead to chronic cough, shortness of breath, occupational asthma, bronchospasm, and anaphylactoid reactions. Chronic deposition of Cr^{6+} particles may also lead to pulmonary fibrosis and pneumoconiosis.

Studies of chromate workers indicate a significantly increased risk of lung cancer in those individuals exposed to Cr^{6+} compounds. The latency between exposure and development of lung cancer ranges from 13–30 years, although, cases occurring after as few as 2 years have been reported.

Because Cr^{3+} is a sensitizing agent, occupational exposure to Cr^{3+} may lead to contact dermatitis (dermatitis toxicosis) in 10–20% of chromium workers. Similarly, chromium-containing gaming table felt has led to hand dermatitis referred to as "blackjack disease," and to painless, scarring, skin ulcerations ("chrome holes").

DIAGNOSTIC TESTING

Chromium is detectable in blood, urine, and hair of exposed individuals. Because of the great difficulty in speciation, differentiation between Cr^{3+} and Cr^{6+} is generally not performed; instead, the total chromium concentration is generally reported. The reported normal serum and urine chromium concentrations in unexposed people have varied by more than 5000-fold over the last 50 years. There is no single reference range for either serum, blood, or urine chromium concentrations in normal subjects. Chromium is distributed evenly between the serum and erythrocytes. Serum chromium concentrations reflect recent exposure to both Cr^{3+} and Cr^{6+}. Blood chromium concentrations, however, are indicative only of recent Cr^{6+} exposure, because of the inability of Cr^{3+} to cross the red blood cell (RBC) membrane. Serum concentrations of people without occupational exposure to chromium are reported to be from 0.05 μg/L (1 nmol/L) to more than 2.8 μg/L (56 nmol/L). Although urine chromium concentrations reflect the acute absorption of chromium over the previous 1–2 days, wide individual variation in metabolism and total-body burden limit the value of urinary chromium monitoring. Urinary chromium concentrations in persons without occupational exposure to chromium are likely less than 1 μg/g creatinine. Hair and nail samples are not reliable indicators of exposure to chromium because of the difficulty distinguishing between chromium contamination of the hair sample and chromium incorporated into the hair during protein synthesis.

After confirmed or suspected chromium exposure, complete blood count, serum electrolytes, blood urea nitrogen, creatinine, urinalysis, and liver enzymes should be performed.

MANAGEMENT

After adequate airway, breathing, and circulatory support have been addressed, attention should be given to decontamination. Because of its very limited toxicity, patients with exposure to Cr^{3+} compounds should require

limited decontamination measures. However, as other ingestants could be present, standard gut decontamination with activated charcoal should be considered.

Hexavalent chromium is corrosive and profuse vomiting and hematemesis usually follow acute ingestions. Nasogastric lavage may be beneficial after Cr^{6+} ingestions if the patient presents to the emergency department within 1–2 hours of exposure. There are no data regarding the use of activated charcoal in acute chromium ingestions. However, as activated charcoal is a relatively benign therapy and other coingestants may be adsorbed by activated charcoal, a single dose of activated charcoal should be considered.

Although *N*-acetylcysteine increases the excretion of chromium in rats, no human data exist for this therapy. The administration of oral *N*-acetylcysteine for acute chromium toxicity is generally advisable. Similarly, although ascorbic acid increases the reduction of Cr^{6+} to Cr^{3+} in vitro, there are no data to substantiate its beneficial use in acute toxicity.

None of the currently available chelating agents appear efficacious at either lowering serum or blood chromium concentrations, or ameliorating chromium toxicity in experimental models.

Hemodialysis, hemofiltration, and peritoneal dialysis are ineffective in removing chromium. Exchange transfusions may rapidly reduce blood chromium concentrations, but there are no data suggesting that clinical outcomes are positively affected.

89 Cobalt

HISTORY AND EPIDEMIOLOGY

The main industrial use of cobalt (Co) is the formation of hard, high-speed, high-temperature cutting tools. When aluminum and nickel are blended with cobalt, an alloy (alnico) with magnetic properties is formed. Other uses for Co include electroplating because of its resistance to oxidation and as an artist's pigment because of its bright blue color.

Cobalt chloride was combined with iron salts and marketed in the 1950s for the treatment of anemia, a practice that continued until the 1970s. The radioactive isotope, cobalt-60 (^{60}Co), is used in radiotherapy.

Epidemics of cardiomyopathy and goiter termed "beer drinkers' cardiomyopathy" and "cobalt-induced goiter" occurred in the 1960s and the 1970s when cobalt sulfate was added to beer as a foam stabilizer.

CHEMISTRY

Cobalt occurs in elemental, inorganic, and organic forms. The clinical effects of each form are less well defined than the effects of mercury and arsenic. Elemental cobalt (Co^0) toxicity is reported through both inhalational and oral exposures. Inorganic Co salts most commonly occur in one of two oxidation states: cobaltous (Co^{2+}) or cobaltic (Co^{3+}). Cobaltous salts were used for the treatment of anemia and were associated with the "beer drinkers' cardiomyopathy." Organic cobalt exposure results from cyanocobalamin (vitamin B_{12}) ingestion but because of its limited oral absorption and its rapid renal elimination, it is considered of low toxicity.

TOXICOKINETICS

Oral absorption of Co oxides, salts, and metals is highly variable, with a reported bioavailability of 5–45%. Both iron deficiency and iron overload enhance radiolabeled $^{57}CoCl_2$ absorption from the small bowel. Inhaled cobalt oxide is approximately 30% bioavailable. The volume of distribution and elimination half-life are not defined. Most (50–88%) absorbed cobalt (organic and inorganic) is eliminated renally, and the remainder is eliminated in the feces.

PATHOPHYSIOLOGY

Like most other metals, cobalt is a multiorgan toxin. $CoSO_4$ inhibits several key enzyme systems and interferes with initiation of protein synthesis. Polynucleotide phosphorylase, an essential enzyme in RNA synthesis, requires Mg^{2+} to function normally. The enzyme functions at 50% of normal in the presence of $CoSO_4$. It is hypothesized that Co^{2+} is capable of displacing Mg^{2+}, the normally required cofactor, from the cofactor site of the enzyme.

$CoCl_2$ increases the rate of glycolysis while it decreases oxygen consumption, suggesting that cobalt may inhibit aerobic metabolism. In the presence of reduced form of nicotinamide adenine dinucleotide (NADH), Co^{2+} is a potent inhibitor of α-ketoglutarate dehydrogenase, a mitochondrial Krebs cycle enzyme. Cobalt may also complex with the reduced form of α-lipoic acid,

thereby interfering with the Krebs cycle. Moreover, cobalt salts are capable of inhibiting dihydrolipoic acid by complexing with its sulfhydryl groups. These reactions result in the inability to convert both pyruvate into acetyl-coenzyme A (CoA) and α-ketoglutarate into succinyl-CoA. These two enzymes are integral in the efficient transition from anaerobic glycolysis to the Krebs cycle and for the Krebs cycle to produce reducing equivalents.

Additionally, as cobalt is capable of accepting an electron, it can participate in oxidation-reduction (redox) cycling and produce free radicals in the lung. $CoCl_2$ also inhibits tyrosine iodinase, the enzyme responsible for combining iodine (I_2) with tyrosine to form monoiodotyrosine in the first step in the synthesis of thyroid hormone. Thus inhibition of tyrosine iodinase results in a decrease in triiodothyronine (T_3) and thyroxine (T_4).

Multiple animal models demonstrate that $CoCl_2$ administration results in reticulocytosis, polycythemia, and erythropoiesis. Although the pathogenesis of these events remains largely unknown, one theory is that cobalt binds to iron-binding sites such as transferrin, resulting in impaired oxygen transport to renal cells, which, in turn, induces erythropoietin production.

CLINICAL EFFECTS AND TOXICITY

The minimal acute toxic dose of cobalt compounds is not well defined. Patients with "beer drinkers' cardiomyopathy" received an average daily dose of 6–8 mg of $CoSO_4$ (over weeks to months), whereas infants being treated for anemia who received much higher daily cobalt doses of an iron-cobalt preparation (40 mg of $CoCl_2$ and 75 mg of $FeSO_4$), for 3 months did not develop toxic effects. The inconsistency suggests that multiple factors are responsible including a specific role for the NADH excess associated with ethanol metabolism.

CLINICAL MANIFESTATIONS

Acute Exposure

"Beer Drinkers' Cardiomyopathy"

A history of beer drinking, tachycardia, dyspnea, and lactic acidosis without congestive heart failure characterize this syndrome. A mortality rate of 38% was reported and typically occurred within 72 hours of presentation. Other clinical findings included polycythemia and low voltage ECGs.

Endocrine

Both acute and chronic cobalt exposures are associated with thyroid hyperplasia and goiter. Occupational data also suggests that inhalational exposure to cobalt metals, salts, and oxides may result in abnormalities in thyroid function. Among decedents from beer drinkers' cardiomyopathy, 11 of 14 had abnormal thyroid histology consisting of follicular cell abnormalities and colloid depletion.

Hematologic

Patients receiving $CoCl_2$ have increased hemoglobin, hematocrit, and red blood cells.

Other

Gastrointestinal distress is reported following the ingestion of "therapeutic" doses of cobalt salts, as well as elemental cobalt. Decreased proprioception,

impaired cranial nerve VIII function, and nonspecific peripheral nerve findings are reported with acute oral $CoCl_2$ exposures.

Chronic

Pulmonary

Two pulmonary diseases are associated with cobalt exposure: asthma and "hard-metal disease." Occupational asthma is reported in hard metal workers with a prevalence of 2–5%. Cobalt-associated pulmonary toxicity was first noted in tungsten-carbide workers, and was subsequently referred to as "hard-metal disease." Signs and symptoms of hard-metal disease include upper respiratory tract irritation, exertional dyspnea, severe dry cough, wheezing, and interstitial lung disease ranging from alveolitis to progressive fibrosis.

Renal

A single report associates reversible renal tubular necrosis with the chronic administration of $CoCl_2$ as treatment for anemia.

Dermatologic

In a study of 1782 construction workers, 23.6% developed dermatitis and 11.2% developed oil acne while using cobalt-containing cement, fly ash, or asbestos. As in hard-metal disease, it is difficult to isolate cobalt as the sole contributor to the development of dermatitis.

Reproductive

In pregnant rats, $CoCl_2$ exposure neither results in teratogenicity nor fetotoxicity. In mice, chronic exposure to cobalt results in impaired spermatogenesis and decreased fertility without affecting follicular stimulating hormone (FSH) or leuteinizing hormone (LH), whereas acute exposures did not demonstrate similar reproductive effects. Despite these findings, there are no reported human cases that associate cobalt exposure with teratogenicity or impaired fertility.

Carcinogenesis

The International Agency for Research on Cancer considers cobalt and cobalt-containing compounds possibly carcinogenic to humans. This is based solely on animal experiments demonstrating soft-tissue sarcomas following the injection of $CoCl_2$. Although case reports and cohort studies suggest that pulmonary exposure to Co^{2+} increases the risk for lung cancer, these studies were unable to control for other known carcinogens, such as arsenic. In a large cohort study, that followed more than 1100 workers for more than 38 years, there was no increase in the prevalence of lung cancer.

DIAGNOSTIC TESTING

Body fluid cobalt concentrations are not readily available and therefore cannot be used to direct emergent clinical care. Adjunctive testing that might support a clinical diagnosis of cobalt toxicity should include complete blood count (CBC), reticulocyte count, erythropoietin (EPO) concentration, and thyroid-stimulating hormone (TSH) concentration. The results of these tests might reflect the level of exposure or potential toxicity discussed above.

Cardiac Studies

Electrocardiogram, echocardiogram, and radionuclide angiocardiography with ^{99}Tc are useful screening tests for detecting abnormalities associated with cobalt cardiomyopathy and/or pulmonary hypertension caused by hard-metal disease.

Pulmonary Testing

Patients with hard-metal lung disease may demonstrate bilateral upper lobe interstitial lung disease on chest radiograph. Pulmonary function testing may show decreased vital capacity and a decrease in transfer factor for carbon monoxide (TLCO) which may identify patients at risk for pulmonary fibrosis. A definitive diagnosis of hard-metal disease requires a tissue sample with findings of multinucleated giant cells in the setting of interstitial pulmonary fibrosis.

Cobalt Testing

Published literature on "normal concentrations" is fraught with variability, which may reflect differences in the population under study and the techniques for measurement. Normal serum concentrations of cobalt are frequently reported as 0.1–1.2 μg/L. In comparison, a single, acutely poisoned patient had a reported serum concentration of 41 μg/L. Normal reference urine cobalt concentrations are between 0.1–2.2 μg/L. In contrast, an acute elemental cobalt ingestion resulted in a concentration of 1700 μg/L on a spot urinalysis several days after the exposure. Exposed workers, without clinical disease, have reported spot urine concentrations that range from 10 μg/L to several hundred μg/L.

TREATMENT

Acute Management

It is reasonable to conclude that the same decontamination principles used for other metals apply to cobalt. No study has examined the benefit of gastric emptying, activated charcoal, or whole-bowel irrigation. An attempt at whole-bowel irrigation (WBI) for radiopaque solid forms of cobalt should be made prior to endoscopic or surgical removal. Regardless of the decontamination procedure used, chelation therapy should not be initiated until the gastrointestinal burden has been removed.

Unfortunately, the data on chelation therapy is limited to animal models and a single human case report. Several agents—*N*-acetylcysteine (NAC), succimer, ethylenediaminetetraacetic acid (EDTA), glutathione, and diethylenetriaminepentaacetic acid (DTPA)—enhance urinary and fecal elimination of cobalt. Na_2EDTA was effective in reducing mortality. Dimercaprol (BAL) is unable to chelate Co^{2+} in vitro and was ineffective in an animal model.

Human chelation data is available from a single pediatric case. Five days of 50 mg/kg/d of IV $CaNa_2EDTA$ enhanced renal elimination of cobalt, and the metabolic acidosis and the cardiac dysfunction also resolved simultaneously. Based on this single case report, several animal studies, and safety profiles, $CaNa_2EDTA$ and NAC can be used as antidotal therapy. Indications for treatment should include patients who demonstrate end-organ manifestations of toxicity such as acidemia, cardiac failure, pericardial effusion, clinically sig-

nificant goiter, and hyperviscosity syndrome. $CaNa_2EDTA$ should be dosed as is in lead poisoning, and NAC should be dosed as it would be for acetaminophen toxicity. The 21-hour intravenous NAC protocol should be initiated and continued as in the case of fulminant hepatic failure (see Antidotes in Brief: *N*-Acetylcysteine). Thiamine hydrochloride should be administered to all patients. The daily administration of 100 mg of parenteral thiamine can be initiated with increasing doses to 100 mg every hour for life-threatening manifestations (cardiac failure and metabolic acidosis) (see Antidotes in Brief: Thiamine Hydrochloride) to protect against concomitant thiamine deficiency (beriberi).

90 Copper

Copper sulfate is used as a fungicide, algicide, and to eradicate tree roots that invade septic, sewage, and drinking water systems, and may be found in older home chemistry sets and crystals growing kits. Copper salts are also important as catalysts, particularly in the petroleum industry. Copper is available naturally, either as native copper (elemental copper) or as one of its sulfide or oxide ores. Acute copper poisoning is nearly always a result of ingestion of ionic copper, most commonly in the salt form, such as copper sulfate, although other routes of exposure are reported. Salts that are water soluble are likely to be more toxic than those that are not.

The Environmental Protection Agency guidelines permit up to 1.3 mg/L of copper in drinking water, although in some areas, concentrations may intermittently be as high as 60 mg/L. Copper in water may be tasted at concentrations of 1–5 mg/L and a blue-green discoloration is imparted when the concentrations are greater than 5 mg/L. Acute gastrointestinal symptoms occur when water contains more than 25 mg/L, although concentrations as low as 3 mg/L are often considered toxic.

CHEMICAL PRINCIPLES

Metallic copper (Cu^0) has an oxidation state of zero and although not in itself poisonous, it may react in acidic environments to release copper ions. In copper sulfate, also known as cupric sulfate, the copper atom is in the +2 oxidation state.

PHARMACOLOGY AND PHYSIOLOGY

Copper is one of eight essential metals that our body stores in milligram amounts (100–150 mg). Copper is absorbed by an active process involving a Cu-adenosine triphosphatase (ATPase) in the small intestinal mucosal cell membrane. The gastrointestinal absorption varies with the copper intake and the food source, and is as low as 12% in patients with high copper intake. In the presence of damaged mucosa, such as following acute overdose, the fractional absorption is likely to be significantly higher. Once absorbed, copper is rapidly bound to carriers such as albumin, ceruloplasmin, and amino acids, such as histidine, for transport to the liver and other tissues. Its half-life in the plasma is approximately 15 minutes. After being released locally in the reduced form from its carrier, copper uptake by the hepatic cells occurs via a specific uptake pump.

Some copper is released from the liver, bound primarily to ceruloplasmin, an α_2-sialoglycoprotein with a molecular weight of 132,000 daltons. Ceruloplasmin-bound copper accounts for approximately 90–95% of serum copper. Ceruloplasmin is a multifunctional protein that binds 6 atoms of copper per molecule. Copper bound to this carrier has a plasma half-life of approximately 24 hours. Ceruloplasmin is also involved in the mobilization of iron from its storage sites and it serves an analogous role as a ferroxidase during the ferrous–ferric conversion. The amount of unbound copper in the blood under normal circumstances is well below 1%.

The volume of distribution of copper is 2.0 L/kg and the $t_{1/2}$ of erythrocyte copper is 26 days. The elimination of copper occurs predominantly through biliary excretion following complexation with ceruloplasmin. Biliary excretion approximates gastrointestinal absorption, and averages 2000 μg/24 h. Renal elimination under normal conditions is trivial, accounting for approximately 5–25 μg/24 h.

TOXICOLOGY AND PATHOPHYSIOLOGY

Redox Chemistry

In acute overdose, a high fraction of the serum copper remains bound to low-affinity proteins, such as albumin, and thus is biologically active. Because, as a transition metal, copper is capable of assuming one of several different oxidation, or valence, states, it is an active participant in oxidation–reduction, or redox, reactions. In particular, participation in the Fenton reaction and Haber-Weiss cycle explains the toxicologic effects of copper as a generator of oxidative stress and inhibitor of several key metabolic enzymes (Chap. 13).

CLINICAL MANIFESTATIONS

Acute Copper Salt Poisoning

Gastrointestinal irritation, including abdominal pain, hemorrhage, and perforation, is the most common initial manifestation of copper salt poisoning. Blue coloration of the vomitus may occur following the ingestion of certain copper salts, particularly copper sulfate. Blue vomitus is not, however, pathognomonic for copper poisoning; it also occurs in patients who ingest boric acid, methylene blue, and food dyes. Other common symptoms include retrosternal chest pain and a metallic taste. The lethal dose of ingested copper sulfate is suggested to be 0.15–0.3 g/kg, but this is obviously unverified.

The liver receives the initial and most substantial exposure to ingested copper. Consequently, hepatotoxicity is a frequent, although rarely an isolated, manifestation of acute copper sulfate poisoning. Jaundice, while among the most common clinical and biochemical findings following overdose, may be hepatocellular or hemolytic.

Hemolysis is more common than hepatotoxicity, and is present in most patients with liver damage. Copper-induced hemolysis often occurs rapidly following exposure and may be severe. Accounting for the early hemolysis, copper directly oxidizes the erythrocyte membrane, thereby initiating red cell lysis. This is distinct from the Heinz body hemolysis typical of most other oxidant stressors. In most reported cases, the discovery of significant methemoglobinemia occurs early in the patient's clinical course and is rapidly followed by hemolysis.

Renal and pulmonary toxicity occur occasionally and represent extraerythrocytic manifestations of the oxidative effects of the copper ions. In spite of massive intravascular hemolysis, hemoglobinuric renal failure is rare in patients who receive adequate volume-replacement therapy.

Hypotension and cardiovascular collapse occur in patients with the most severe poisoning and is likely multifactorial in origin. The severity and poor patient outcome despite appropriate volume loading suggests that the direct effects of copper on vascular and cardiac cells are also involved. Sepsis caused by transmucosal invasion also may be partially responsible.

Depressed mental status, ranging from lethargy to coma, or seizures following acute poisoning are likely epiphenomena resulting from damage to other organ systems. These findings are particularly common in patients with hepatic failure, and are comparable to those of hepatic encephalopathy from other causes.

Intravenous injection of copper sulfate reportedly produces a clinical syndrome identical to that following ingestion. Inadvertent subcutaneous administration of a veterinary copper glycinate solution produced skin necrosis in the area of the injection.

Chronic Copper Poisoning

Although hepatolenticular degeneration, known as Wilson disease, is a genetic condition of chronic copper overload, there are qualitative similarities to acute copper poisoning. Chronic exogenous copper poisoning is uncommon in adults, but occurs in children in some parts of the world. This condition, commonly called childhood cirrhosis in India and idiopathic copper toxicosis elsewhere, generally occurs in the setting of excessive dietary intake of copper as a result of copper-contaminated water from brass vessels used to store milk.

"Vineyard sprayer's lung," first described in 1969, refers to the occupational pulmonary disease that occurred among Portuguese vineyard workers applying Bordeaux solution, a 1–2% copper sulfate solution neutralized with hydrated lime ($Ca[OH]_2$). The patients developed interstitial pulmonary fibrosis and histiocytic granulomas containing copper. Many of these workers also developed lung adenocarcinoma, hepatic angiosarcoma, and micronodular cirrhosis, raising the possibility of a carcinogenic effect of chronic copper exposure.

Ophthalmic effects of copper salts, primarily following occupational exposure, include irritation of the corneal, conjunctival, or adnexal structures.

DIAGNOSTIC TESTING

Real-time analytical testing for copper is impractical and almost all management decisions must be based on clinical criteria. Copper concentrations are often obtained for confirmatory or investigative purposes. Although never adequately studied, whole-blood copper concentrations may correlate better with clinical findings than serum copper concentrations. However, although there is a statistical relationship between the whole-blood copper concentrations and the severity of poisoning, there is little correlation between clinical findings at any given copper concentration, regardless of what biologic tissue is measured. Occasionally, serum copper concentrations reveal a secondary rise, likely because of release during hepatocellular necrosis.

Reported serum copper concentrations in patients with hemolysis range from 96–747 μg/dL. Serum copper concentrations in 11 patients with copper-induced acute renal failure ranged from 115–390 μg/dL. The normal urinary copper excretion per 24 hours is approximately 25 μg, and is reportedly as high as 628 μg/24 h in patients with acute copper poisoning.

Although serum ceruloplasmin concentrations rise in patients with acute copper poisoning, presumably reflecting increased hepatic synthesis, the ceruloplasmin concentration cannot be used to define the patient's prognosis.

Routine laboratory testing following acute copper salt poisoning should include an assessment for both hemolysis and hepatotoxicity. Differentiation of

these etiologies as a cause for jaundice is made by standard methodology, such as comparison of the bilirubin fractions and an assessment of the hepatic enzymes and hemoglobin. The prothrombin time may be prolonged in the absence of liver injury or disseminated intravascular coagulopathy and may be the result of a direct effect of free copper ions on the coagulation cascade. Also, an assessment of the patient's electrolyte and hydration status is warranted.

MANAGEMENT

Optimal and aggressive supportive care is the cornerstone to the effective management of patients with acute copper poisoning. Attention to antiemetic therapy, fluid and electrolyte correction, and normalization of vital signs are the critical steps before consideration of chelation therapy. Gastrointestinal decontamination is of limited concern as the onset of emesis generally occurs within minutes of ingestion and is often protracted.

Management of the hepatic toxicity requires little more than standard supportive care. *N*-acetylcysteine is unstudied, although it may be useful and should be given intravenously in the presence of hepatotoxicity if there are no contraindications. Liver transplantation for liver failure should be considered if applicable.

Chelation Therapy

Chelation therapy should be initiated when hepatic or hematologic complications are present or the patient is severely poisoned. Studies on the efficacy of chelation therapy following acute copper salt poisoning are limited and extrapolation from the treatment of Wilson disease is common.

Most patients with copper poisoning are initially treated with intramuscular British anti-Lewisite (BAL). Although BAL may be less effective, its use is appropriate in patients in whom vomiting or gastrointestinal injury prevents oral D-penicillamine administration. When tolerated, D-penicillamine therapy should be started simultaneously or shortly after the initiation of therapy with BAL.

Edetate calcium disodium ($CaNa_2EDTA$) reduces the oxidative damage induced by copper ions in experimental models. However, it does not greatly enhance the elimination of copper when used for the chelation of other metals

D-Penicillamine (Cuprimine), a structurally distinct metabolite of penicillin, is an orally bioavailable monothiol chelating agent. D-Penicillamine is effective in preventing copper-induced hemolysis in patients with Wilson disease. The D-penicillamine–copper complex undergoes rapid renal clearance in patients with competent kidneys. The use of D-penicillamine has not been formally studied in patients with acute copper salt poisoning, but case studies and animal models suggest that copper elimination is enhanced. The recommended dose is 1–1.5 g/d given orally in 4 divided doses. D-Penicillamine is also indicated for the treatment of chronic exogenous copper poisoning, such as Indian childhood cirrhosis. Initiation early in the course of the disease, along with discontinuation of the exposure, is associated with hepatic recovery and dramatically improved survival rates.

D-Penicillamine is associated with several significant complications with chronic use, including aplastic anemia, agranulocytosis, and renal and pulmonary disease. However, in the brief treatment necessary for acutely poisoned patients, the major risk is the potential for hypersensitivity reactions that occur in 25% of patients who are penicillin allergic.

Succimer enhances copper elimination in a murine model, although it is unstudied in human copper poisoning. Given its ease of use, relative safety, and benefit in experimental models, succimer can be used in lieu of D-penicillamine in patients with mild or moderate poisoning. Under these circumstances, the use of standard lead poisoning dosing regimens is warranted (Chap. 91 and Antidote in Brief: Succimer).

Dimercaptopropane sulfonate (DMPS) worsens copper-induced hemolysis in vitro. Because an adequate analysis of risk versus benefit is unavailable, DMPS should not be used to chelate copper-poisoned patients at this time.

Trientine and zinc, oral agents used for patients with Wilson disease, have not been studied in patients with acute copper poisoning and have no known role.

Extracorporeal Elimination

Exchange transfusion is of undefined, but probably limited benefit in acute copper sulfate poisoning. Hemodialysis and peritoneal dialysis appear to be of little clinical use.

Pregnancy

There are no controlled data on the treatment of acute copper poisoning in pregnancy. The available data on pregnant women with Wilson disease document that D-penicillamine is teratogenic and that zinc may be the preferred therapeutic agent.

91 Lead

PHYSICAL PROPERTIES

Lead is a silvery-gray, soft, metal that is widely distributed geologically. In compounds, lead assumes valence states of +2 and +4. Inorganic lead compounds may be brightly colored and vary widely in water solubility; several are used extensively as pigments in paints, such as lead chromate (yellow) and lead oxide (red). Lead also forms organic compounds, of which tetramethyl and tetraethyl lead were used commercially as gasoline additives. There is no known physiologic role for lead.

HISTORY AND EPIDEMIOLOGY

Industrial Applications

Lead's low melting point and malleability made it one of the first metals smelted and used by human society. Lead-based ocher paints are believed to date to approximately 40,000 B.C. Ancient Egyptians and Hebrews used lead, and the Phoenicians established lead mines in Spain circa 2000 B.C. Today, lead is the most widely used nonferrous metal, with global production on the order of 9 million tons annually. Use of both lead-based paint for house paint and leaded gasoline has been essentially eliminated by regulation in the United States since the 1980s, but persistence of lead paint in older homes still constitutes an enormous environmental challenge.

History of Lead-Related Health Effects

The problem of human poisoning from lead, known as plumbism, dates back to antiquity. Dioscorides, a Greek physician in the 2nd century B.C., observed that lead makes the mind "give way." Modern authors have suggested that extensive use of sapa in Roman aristocratic society contributed to the downfall of Roman dominance. The reproductive effects of lead poisoning were noted by the turn of the 20th century, including the high rate of stillbirths, infertility, and abortions among women in the pottery industry, or who were married to pottery workers. The modern history of childhood plumbism can be traced to the recognition of lead-paint poisoning in Brisbane, Australia, in 1897.

Sources of Human Exposure

Numerous sources of lead exposure exist, and can be generally classified as environmental, occupational or "exotic." *Environmental* exposures affect the entire population, particularly young children. Although paint-derived lead exposure may result from pica for some children, most lead paint exposure in childhood relates to the crumbling, peeling, flaking, or chalking of aging paint. Adults with *occupational* and persons of all ages with *recreational* or *exotic* exposures to lead constitute another large group of persons at risk. It is estimated that more than 1 million workers in the United States, employed in more than 100 occupations, are exposed to lead. The most important route of absorption in occupational settings is inhalation of lead dust and fumes. Finally, numerous additional *exotic sources* are also reported sporadically, such

as exposures to contaminated folk medications or cosmetics, ingested lead foreign bodies, or retained bullets.

Prevalence

The US Centers for Disease Control and Prevention (CDC) recently estimated that blood lead concentrations (BLLs) are >9 μg/dL in 434,000 children 1–5 years old, and that approximately 10,000 adult workers are reported each year with BLLs >24 μg/dL. The CDC has also reported that children enrolled in Medicaid had a prevalence of elevated BLLs three times greater than those not in Medicaid. Refugee, immigrant, and foreign-born adoptee children remain at particularly high risk. Remarkable cases of extremely elevated BLLs (>100 μg/dL) are still detected on routine screening.

TOXICOLOGY

Pharmacokinetics

Inorganic Lead

Absorption Gastrointestinal (GI) absorption is less efficient than pulmonary absorption. Adults absorb an estimated 10–15% of ingested lead in food, and children have a higher GI absorption rate, averaging 40–50%. The overall absorption of inhaled lead averages 30–40%. Cutaneous absorption of inorganic lead is low. Alkyl leads may have appreciable cutaneous absorption that is capable of causing toxicity. Lead readily crosses the placental barrier throughout gestation, and lead uptake is cumulative until birth. Breast milk from heavily exposed mothers may likewise be a potential source of lead exposure.

Distribution Absorbed lead enters the bloodstream where at least 99% is bound to erythrocytes. Lead is distributed into both a relatively labile soft-tissue pool and into a more stable bone compartment. In adults, approximately 95% of the body lead burden is stored in bone, versus only 70% in children. The remainder is distributed to the major soft-tissue lead-storage sites, including liver, kidney, bone marrow, and brain. Lead preferentially concentrates in gray matter and certain nuclei, and is of particular toxicologic importance. The highest brain concentrations are found in hippocampus, cerebellum, cerebral cortex, and medulla. Unlike soft-tissue storage, bone lead accumulates throughout life. Total-body accumulation of lead ranges from 200 mg to more than 500 mg in workers with heavy occupational exposure.

Excretion Absorbed lead that is not retained is excreted primarily in urine (approximately 65%) and bile (approximately 35%). Children excrete less of their daily uptake than adults, with an average retention in adults of 1–4% versus 33% in children. Biologic half-lives for lead are estimated as follows: blood (adults, short-term experiments), 25 days; blood (children, natural exposure), 10 months; soft tissues (adults, short-term exposure), 40 days; bone (labile, trabecular pool), 90 days; and bone (cortical, stable pool), 10–20 years.

Organic Lead

Tetraethyl lead is lipid soluble, easily absorbed through intact skin, and distributed widely to lipophilic tissues, including the brain. Tetraethyl lead is metabolized to triethyl lead, which is believed to be the major toxic compound. Alkyl leads slowly release lead as the inorganic form, with subsequent kinetics as noted above.

PATHOPHYSIOLOGY

General Effects

Lead is a complex toxin with numerous pathophysiologic effects in many organ systems. At the biomolecular level, lead functions in three general ways. First, its affinity for biologic electron-donor ligands, especially sulfhydryl groups, allows it to bind and impact numerous enzymatic, receptor, and structural proteins. Second, lead is chemically similar to calcium and interferes with numerous metabolic pathways, particularly in mitochondria and in second-messenger systems, regulating cellular energy metabolism. Third, lead exhibits mutagenic and mitogenic effects in mammalian cells in vitro and is carcinogenic in rats and mice.

Neurotoxicity

The neurotoxicity of lead involves several mechanisms, including apoptosis, excitotoxicity, adverse influence on neurotransmitter and second-messenger function, mitochondrial injury, cerebrovascular endothelial damage, and impaired development and function of both oligodendroglia and astroglia, although particularly the former, with resultant abnormal myelin formation. Peripheral neuropathy is a classic effect of occupational lead poisoning. In animal models, it is associated with Schwann cell destruction, segmental demyelination, and axonal degeneration. Sensory nerves are less affected than motor nerves.

Hematologic

Lead is a potent inhibitor of several enzymes in the heme biosynthetic pathway (Chap. 24). It also induces a defect in erythropoietin function secondary to associated renal damage. Shortened erythrocyte life span is believed to be caused by increased membrane fragility. Inhibition of pyrimidine-5′-nucleotidase produces basophilic stippling in erythrocytes from failed degradation of nuclear RNA.

Renal

Lead nephropathy produces a Fanconilike syndrome of aminoaciduria, glycosuria, and phosphaturia. These changes are believed to be related to disturbed mitochondrial function. Lead decreases renal uric acid excretion, with resulting elevated blood urate concentrations and urate crystal deposition in joints.

Cardiovascular

The most important manifestation of lead toxicity on the cardiovascular system is hypertension. This is likely caused by altered calcium-activated changes in contractility of vascular smooth muscle cells, secondary to decreased Na^+-K^+-adenosine triphosphatase (ATPase) activity and stimulation of the Na^+-Ca^{2+} exchange pump.

Reproductive System

Impairment of both male and female reproductive function is associated with overt plumbism.

Endocrine

Reduced thyroid and adrenopituitary function are found in adult lead workers. Children with elevated lead concentrations have depressed secretion of human growth hormone and insulinlike growth factor.

Skeletal System

Bone metabolism is adversely affected by lead. Bands of increased metaphyseal density seen on radiographs of long bones in young children with heavy lead exposure demonstrate increased calcium deposition in the zones of provisional calcification. Impaired bone growth and shortened stature are associated with childhood lead poisoning.

Gastrointestinal

Gastrointestinal effects may be partly explained by spasmodic contraction of intestinal wall smooth muscle, analogous to that believed to occur in vascular walls.

CLINICAL PRESENTATION

Inorganic Lead

The numerous observed lead-induced pathophysiologic effects accurately predict that the clinical manifestations of lead poisoning are diverse. These manifestations of lead toxicity are often characterized as falling into distinct syndromes of acute and chronic symptomatology. By far, the most important contexts of lead toxicity in the United States today are related to chronic environmental exposure in children and chronic occupational exposure in adult workers. These are sufficiently distinct in epidemiology, clinical manifestations, and current recommended management approaches that they are described separately (Tables 91–1 and 91–2). Severe symptomatic poisoning is rare in recent years among persons of all ages, although it is still reported. It should be first reemphasized that the occurrence of overt clinical symptoms in lead-exposed persons is, in most cases, the culmination of a long history of lead exposure. As total dose increases, these symptoms are almost always preceded first by measurable biochemical and physiologic impairment, followed, in turn, by subtle prodromal clinical effects that may only become apparent in hindsight.

Symptomatic Children

Acute lead encephalopathy is the most severe presentation of pediatric plumbism. It may be associated with cerebral edema and increased intracranial pressure, pernicious vomiting and apathy, bizarre behavior, loss of recently acquired developmental skills, ataxia, incoordination, seizures, altered sensorium, or coma. Physical examination may reveal papilledema, oculomotor or facial nerve palsy, diminished deep-tendon reflexes, or other evidence of increased intracranial pressure. Encephalopathy usually is associated with BLLs >100 μg/dL, although it is reported with BLLs as low as 70 μg/dL. Many patients seek medical advice for vomiting and lethargy during the 2–7 days prior to onset of encephalopathy.

Subencephalopathic symptomatic plumbism usually occurs in children 1–5 years old and is associated with BLLs >70 μg/dL, but may occur with concen-

TABLE 91–1. Clinical Manifestations of Lead Poisoning in Children

Clinical Severity	Typical Blood Lead Concentrations (μg/dL)
Severe	
CNS: Encephalopathy (coma, altered sensorium, seizures, bizarre behavior, ataxia, apathy, incoordination, loss of developmental skills, papilledema, cranial nerve palsies, signs of increased ICP) GI: Persistent vomiting Heme: Pallor (anemia)	>70–100
Mild/moderate	
CNS: Hyperirritable behavior, intermittent lethargy, decreased interest in play, "difficult" child GI: Intermittent vomiting, abdominal pain, anorexia	50–70
Asymptomatic	
CNS: Impaired cognition, behavior PNS: Impaired fine-motor coordination Misc: Impaired hearing, growth	0–49

CNS = central nervous system; GI = gastrointestinal; Heme = hematologic; ICP = intracranial pressure; Misc = miscellaneous; PNS = peripheral nervous system.

TABLE 91–2. Clinical Manifestations of Lead Poisoning in Adults

Clinical Severity	Typical Blood Lead Concentrations (μg/dL)
Severe	
CNS: Encephalopathy (coma, seizures, obtundation, delirium, focal motor disturbances, headaches, papilledema, optic neuritis, signs of increased ICP) PNS: Footdrop, wristdrop GI: Abdominal colic Heme: Pallor (anemia) Renal: Nephropathy	>100
Moderate	
CNS: Headache, memory loss, decreased libido, insomnia GI: Metallic taste, abdominal pain, anorexia, constipation Renal: Nephropathy with chronic exposure Misc: Mild anemia, myalgias, muscle weakness, arthralgias	70–100
Mild	
CNS: Tiredness, somnolence, moodiness, lessened interest in leisure activities Misc: Impaired psychometrics, reproduction; hypertension	40–69

CNS = central nervous system; GI = gastrointestinal; Heme = hematologic; ICP = intracranial pressure; Misc = miscellaneous; PNS = peripheral nervous system.

trations as low as 50 μg/dL. Unfortunately, common complaints in healthy children of this age ("terrible two's," with functional constipation and who don't eat as much as parents expect) often overlap with the milder range of reported symptoms of lead poisoning.

Asymptomatic Children

Children with *elevated body lead burdens but without overt symptoms* represent the largest group of persons believed to be at risk of chronic lead toxicity. The subclinical toxicity of lead in this population centers around subtle effects on growth, hearing, and neurocognitive development. There is a significant inverse association between lead exposure and IQ, on the order of 1–2 IQ points for each 10–20 μg/dL increase in BLL.

Adults

Most adult plumbism is related to chronic respiratory exposure, although some authors have used the term *acute poisoning* to include patients with exposure whose symptoms are severe and of relatively recent onset (within 6 weeks of presentation) and whose exposure is relatively brief (average: 1 year or less). Adult patients with severe plumbism often manifest attacks of abdominal colic, are virtually always anemic, and are at significant risk for severe peripheral nerve palsy (eg, wristdrop, footdrop) and nephropathy.

Moderate plumbism in adults typically involves CNS, peripheral nerve, hematologic, renal, gastrointestinal, rheumatologic, endocrine/reproductive, and cardiovascular findings. *Mild plumbism* may manifest minor CNS findings such as changes in mood and cognition. Effects on reproductive function and blood pressure may also be apparent in this range of exposure.

Organic Lead

Clinical symptoms of tetraethyllead (TEL) toxicity are usually nonspecific initially, and include insomnia and emotional instability. Nausea, vomiting, and anorexia may occur. The patient may exhibit tremor and increased deep-tendon reflexes. In more severe cases, these symptoms progress to an encephalopathy with delusions, hallucinations, and hyperactivity, which may resolve or deteriorate to coma and, occasionally, death.

ASSESSMENT

Clinical Diagnosis in Symptomatic Patients

For all patients in whom plumbism is considered based on clinical manifestations, the medical evaluation should first include a comprehensive past medical history, including that of foreign-body ingestions or gunshot wounds with retained bullets. Further inquiry should elicit environmental, occupational, or recreational sources of exposure.

The differential diagnosis of plumbism is broad. Adult patients may be misdiagnosed as having carpal tunnel syndrome, Guillain-Barré syndrome, sickle-cell crisis, acute appendicitis, renal colic, and infectious encephalitis. Children are often initially considered to have viral gastroenteritis, or even to have insidious symptoms passed off as a difficult developmental phase.

Confirmatory blood lead assays are usually not available on an immediate basis. Laboratory findings usually available on an urgent basis include anemia, basophilic stippling, and abnormal urinalysis. In children, lead lines may

be present on skeletal radiographs (Fig. 91–1), and evidence of recent pica for lead paint particles may be present on abdominal radiographs (Fig. 91–2). In both adults and children, the decision to institute empiric chelation treatment should not deter additional emergent diagnostic efforts to exclude or to confirm other important entities while blood lead concentrations are pending.

Diagnostic Laboratory Evaluation

The *whole BLL* is the principal measure of lead exposure available in clinical practice. In any patient suspected of symptomatic plumbism, whole blood should be collected by venipuncture into special lead-free evacuated tubes. For asymptomatic pediatric patients, BLL screening is often performed by capillary blood testing for convenience; however, venous confirmation of elevated capillary lead concentrations, unless extremely high (eg, >69 μg/dL) or the patient is clearly symptomatic, is still considered mandatory prior to chelation or other significant interventions. The *erythrocyte protoporphyrin (EP) concentration* test reflects lead's inhibition of the heme synthesis pathway (Chap. 24) and had been used as a screening tool in the past, but is no longer considered sufficiently sensitive. The EP concentration may still be useful for tracking response to therapy and in distinguishing acute from chronic lead exposure.

MANAGEMENT

The most important aspect of treatment is removal from exposure to lead. Also, pharmacologic therapy with chelation agents, although a mainstay of therapy

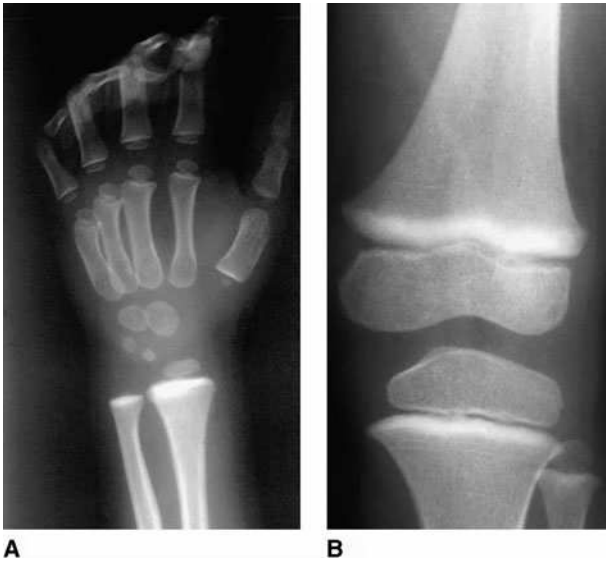

FIG. 91–1. **A.** Radiograph of the wrist reveals increased bands of calcification: "lead lines." *(Courtesy of Department of Radiology, St. Christopher's Hospital for Children, Philadelphia, PA.)* **B.** Similar radiographic findings in another patient at the knee. *(Courtesy of Richard Markowitz, MD, Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA.)*

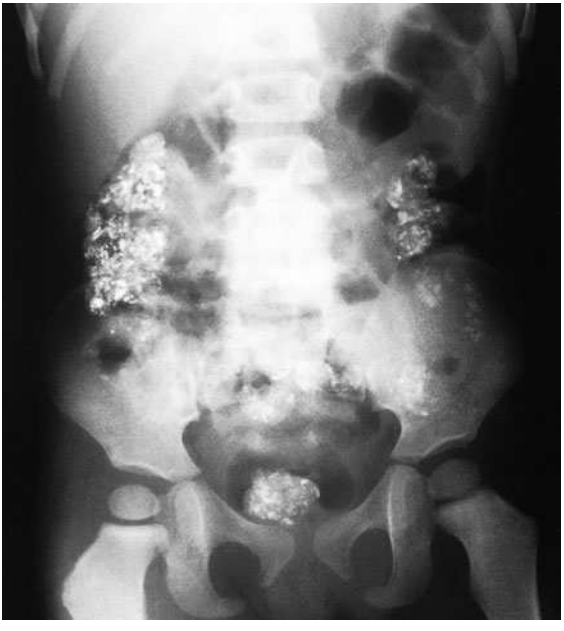

FIG. 91–2. Abdominal radiograph of a child who had massive paint chip ingestion. *(Courtesy of Department of Radiology, St. Christopher's Hospital for Children, Philadelphia, PA.)*

for symptomatic patients, is an inexact science, with numerous unanswered questions despite almost 50 years of clinical use. Chelation therapy increases lead excretion, reduces blood concentrations, and reverses hematologic markers of toxicity during therapy. The institution of effective combination chelation treatment of childhood lead encephalopathy in the 1960s certainly contributed to the dramatic decline in mortality and morbidity. However, chelation therapy for asymptomatic patients with mildly to moderately increased body burdens of lead is less clear. To date, long-term reduction of target tissue lead content or reversal of toxicity is not demonstrated in human trials.

When there is evidence of recent ingestion (such as by history or positive radiograph) some attempt at gastrointestinal decontamination seems warranted. Whole-bowel irrigations with a polyethylene glycol–electrolyte lavage solution seems the most rational method (see Antidotes in Brief: Whole-Bowel Irrigation) since activated charcoal is of little utility.

Chelation Therapy

The indications for and specifics of chelation therapy are determined by patient age, blood-lead concentration, and clinical symptomatology (Table 91–3). Pharmacologic profiles of the available chelators can be found in the Antidotes in Brief sections. Chelation is not a panacea for lead poisoning. It is a relatively inefficient process, with a typical course of therapy decreasing body content of heavy metal by 1–2%.

TABLE 91–3. Chelation Therapy Guidelines[a]

Condition, BPb (μg/dL)	Dose	Regimen/Comments
Adults		
Encephalopathy	BAL 450 mg/m^2/d[a] and	75 mg/m^2 IM every 4 h for 5 d
	$CaNa_2EDTA$ 1500 mg/m^2/d[a]	Continuous infusion or 2–4 divided IV doses for 5 d (start 4 h after BAL)
Symptoms suggestive of	BAL 300–450 mg/m^2/d[a]	50–75 mg/m^2 every 4 h for 3–5 d
encephalopathy or >100	$CaNa_2EDTA$ 1000–1500 mg/m^2/d[a]	Continuous infusion or 2–4 divided IV doses for 5 d (start 4 h after BAL)
		Base dose, duration on BLL, severity of symptoms (see text)
Mild symptoms or 70–100	Succimer 700–1050 mg/m^2/d	350 mg/m^2 tid for 5 d, then bid for 14 d
Asymptomatic and <70	Usually not indicated	Remove from exposure
Children		
Encephalopathy	BAL 450 mg/m^2/d[a]	75 mg/m^2 IM every 4 h for 5 d
	$CaNa_2EDTA$ 1500 mg/m^2/d[a]	Continuous infusion or 2–4 divided IV doses for 5 d (start 4 h after BAL)
Symptomatic or > 69	BAL 300–450 mg/m^2/d[a]	50–75 mg/m^2 every 4 h for 3–5 d
	$CaNa_2EDTA$ 1000–1500 mg/m^2/d[a]	Continuous infusion or 2–4 divided IV doses for 5 d (start 4 h after BAL)
		Base dose, duration on BPb, severity of symptoms (see text)
Asymptomatic: 45–69	Succimer 700–1050 mg/m^2/d	350 mg/m^2 tid for 5 d, then bid for 14 d
	or $CaNa_2EDTA$, 1000 mg/m^2/d[a]	Continuous infusion or 2–4 divided IV for 5 d (see text)
	(*or rarely*, D-penicillamine)	
20–44	Routine chelation not indicated	If succimer used, same regimen as per above group
	(see text)	
	Attempt exposure reduction	
<20	Chelation not indicated	
	Attempt exposure reduction	

BPb = blood lead (μg/dL); EP = erythrocyte protoporphyrin; IM = intramuscular; IV = intravenous; d = day.
[a]Doses expressed in approximate mg/kg: BAL 450 mg/m^2 (24 mg/kg); 300 mg/m^2 (18 mg/kg).
$CaNa_2EDTA$ 1000 mg/m^2 (25–50 mg/kg); 1500 mg/m^2 (50–75 mg/kg); adult maximum 2–3 g/d. Succimer 350 mg/m^2 (10 mg/kg).
Subsequent treatment regimens based on postchelation BLL and clinical symptoms.

Pediatric Therapy

Lead encephalopathy is an acute life-threatening emergency and should be treated under the guidance of a multidisciplinary team in the intensive care unit of a hospital experienced in the management of critically ill children. Chelation is instituted with intramuscular (IM) dimercaprol (BAL) followed 4 hours later by intravenous (IV) edetate calcium disodium ($CaNa_2EDTA$). The delay in initiating $CaNa_2EDTA$ infusion is based on past observations of clinical deterioration in encephalopathic patients treated with $CaNa_2EDTA$ alone. Generally, oral fluids, feedings, and medications are withheld for at least the first several days. Careful provision of adequate intravenous fluids optimizes renal function while avoiding overhydration and the risk of exacerbating cerebral edema. The occurrence of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may be associated with lead encephalopathy, so that urine volume, specific gravity, and serum electrolytes should be closely monitored.

Children with *milder symptoms, or* who are *asymptomatic, with BLL >70 μg/dL*, should be chelated with a regimen similar to that recommended for encephalopathy. The asymptomatic patients in this group might also be adequately treated with 2,3-dimercaptosuccinic acid (succimer) plus $CaNa_2EDTA$, or even succimer alone, but these regimens have not been studied in such children. Intensive care monitoring may be prudent for such patients as well, at least during the initiation of chelation therapy.

Chelation therapy is widely recommended for *asymptomatic children with BLLs between 45 and 70 μg/dL.* Children without overt symptoms may be treated with succimer alone. Home abatement and reinspection should be accomplished before initiation of ambulatory succimer therapy; if this is not feasible, then hospitalization is still warranted. After initial chelation therapy, *decisions to retreat* are based on clinical symptoms and followup BLLs.

The management of *asymptomatic children with BLLs of 20–44 μg/dL* is controversial. The CDC and American Academy of Pediatrics recommend aggressive environmental and nutritional interventions with close monitoring of BLLs, *without routine chelation therapy*, for such children. Nevertheless, there may still be potential indications for occasional chelation treatment in this group, including BLLs at the higher end of the range (eg, 35–44 μg/dL), especially if BLLs remain the same or rise over several months after rigorous environmental controls are instituted in children younger than 2 years old with evidence of biochemical toxicity (elevated EP concentration, after iron supplementation if necessary), or any hint of subtle symptoms.

BLLs of 10–19 μg/dL are defined by the CDC as representing excessive exposure to lead, but do not require chelation therapy. Close monitoring (for the 10–14-μg/dL range) and careful environmental investigation and interventions as necessary (particularly for the 15–19 μg/dL range) are appropriate and sufficient.

Adult Therapy

General Considerations

The first principle in the treatment of adults with lead poisoning is that chelation therapy may not substitute for adherence to Occupational Safety and Health Administration (OSHA) lead standards at the worksite and should

never be given prophylactically. In addition to the guidelines for decreasing lead exposure noted earlier, chelation therapy is indicated in adults with significant symptoms (encephalopathy, abdominal colic, severe arthralgia or myalgia) and evidence of target-organ damage (neuropathy or nephropathy), and possibly in asymptomatic workers with markedly elevated BLLs and/or evidence of biochemical toxicity or increased chelatable lead. Table 91–3 outlines chelation therapy regimens for adults.

Pregnancy, Neonatal, and Lactation Issues

An area of particular concern in the management of adult plumbism involves decisions regarding therapy during pregnancy. Chelation therapy during early pregnancy poses theoretical problems of teratogenicity, particularly that caused by enhanced fetal excretion of potentially vital trace elements, or translocation of lead from mother to fetus. Symptomatic pregnant women with elevated BLLs certainly warrant chelation therapy regardless of these concerns. It should be noted that despite falls in maternal BLL with chelation therapy, newborn BLLs may be considerably higher, and in some cases may approximate the pretreatment maternal BLL, implying limited efficacy for in utero fetal chelation. In general, there currently seems little support for routine chelation therapy in pregnant women who would not otherwise warrant treatment based on their own symptoms or degree of elevated BLL.

Postnatally, infant BLLs may decline over time without chelation, but this occurs very slowly. Postpartum chelation therapy is warranted for neonates, depending on BLLs, as per the guidelines described above for older children. Lastly, the issue of allowing mothers with elevated BLLs to breast-feed their infants may arise. Breast milk analysis may be warranted in such cases, particularly with BLLs of 35 μg/dL or greater, before safely advising continued nursing.

Succimer (2,3-Dimercaptosuccinic Acid)

PHARMACOLOGY

Succimer is the meso form of 2,3-dimercaptosuccinic acid. Because it contains four ionizable hydrogen ions, succimer has four different pK_as—2.31, 3.69, 9.68, and 11.14—with the dissociation of the two lower values representing the carboxyl groups and the two higher values the sulfur groups. Lead and cadmium bind to the adjoining sulfur and oxygen atoms, whereas arsenic and mercury bind to the 2 sulfur moieties, forming pH-dependent water-soluble complexes. Succimer is highly protein-bound to albumin. It is eliminated almost exclusively via the kidney, with only trace amounts (<1%) excreted via feces or expired air. Maximal excretion of succimer occurs in urine specimens collected between 2 and 4 hours after administration.

LEAD

Animal studies demonstrate the ability of succimer to enhance urinary lead elimination and to reduce blood, brain, liver, and kidney lead concentrations with unclear effects on bone lead concentrations. Interestingly, stopping lead exposure reduced blood lead concentrations by 63% and brain concentrations by 34%, compared to pretreatment concentrations. Although a similar end point was achieved with succimer therapy, the total lead removal was greater, with the biggest drop in blood lead concentrations over the first 5 days. Under a variety of experimental conditions in animals, succimer prevents the deleterious effect of lead on heme synthesis, blood pressure, and behavior.

Published studies of the use of succimer in children and adults demonstrate consistent findings. During the first 5 days of chelation, blood lead concentration drops precipitously, by approximately 60–70%. Urinary lead excretion exceeds estimated blood content, suggesting that some lead is being removed from soft tissues. Typically, 2 weeks after the completion of therapy, blood lead concentration rebounds to values 20–40% lower than pretreatment values. The Treatment of Lead-exposed Children (TLC) trial is an ongoing trial that examines the effects of succimer on cognitive development, behavior, stature, and blood pressure in children 1–3 years old with blood lead concentrations between 20 and 44 μg/dL. To date, no clinically significant difference has been demonstrated between succimer-treated children and controls.

Controlled trials are not available in patients with lead encephalopathy and the overall experience with the use of succimer in severely lead-poisoned patients, including those with encephalopathy, is very limited. Declines in blood lead concentration appear comparable to treatment with a combination of dimercaprol (BAL) for 3 days and 5 days of edetate calcium disodium ($CaNa_2EDTA$).

ARSENIC

Animal studies with sodium arsenite and Lewisite demonstrate that succimer improves the LD_{50} (median lethal dose for 50% of test subjects) with a good therapeutic index, lack of redistribution of arsenic to the brain, and reduced kidney and liver arsenic concentrations. A few human case reports attest to the ability of succimer to enhance the urinary excretion of arsenic, but no controlled beneficial

outcome data exist. A comparison of BAL, succimer, and dimercaptopropane sulfonate (DMPS) as arsenic antidotes, demonstrated higher therapeutic indices for succimer and DMPS than for BAL in chronic arsenic poisoning.

MERCURY

Succimer improves survival, decreases renal damage, and enhances elimination of mercury following inorganic mercury and methylmercury exposure in animals. It also enhances the elimination of mercury in humans poisoned with inorganic, elemental, and methylmercury. When succimer was given to victims of an extensive Iraqi methyl mercury exposure, blood methylmercury half-life decreased from 63 days to 10 days. Unfortunately, as above, controlled human trials are lacking.

PHARMACOKINETICS

The pharmacokinetics of a single oral dose of succimer in humans demonstrates that the half-life is 1.5 times longer in children than in adults, and that the distribution of succimer appears to be greater in poisoned patients than in healthy adults. Succimer undergoes an enterohepatic circulation facilitated by gastrointestinal (GI) microflora.

ADVERSE EFFECTS AND SAFETY ISSUES

Succimer is generally well tolerated, with few serious adverse events reported. Common adverse effects are gastrointestinal in nature, including nausea, vomiting, flatus, diarrhea, and a metallic taste in 10–20% of patients. Mild elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are reported. Rarely, chills, fever, urticaria, rash, transient neutropenia, and eosinophilia are reported. A number of studies with succimer demonstrate no rise in urinary zinc, copper, iron, or calcium elimination. An obvious limitation concerning the safety of succimer is that there is still relatively limited clinical experience with the drug, particularly with regard to long-term administration.

One concern with administering succimer orally is that outpatient management might permit continued unintentional lead exposure and the possibility for succimer-facilitated lead absorption. Animal studies suggest that succimer does not promote lead retention in the face of continued exposure unless lead exposure is overwhelming. A radiolabeled lead tracer administered to adult volunteers suggested that succimer increased the net absorption of lead from the gastrointestinal tract and may distribute it to other tissues. More recently, two children with environmental exposure to lead had dramatic rises in blood concentrations while receiving succimer at home. In the event of unintentional exposure to a new lead source, decontamination of the gastrointestinal tract should complement (or even precede) oral succimer.

A case report describes a 3-year-old patient who reportedly ingested 185 mg/kg of succimer and remained asymptomatic. No observed teratogenic effects were noted experimentally when 410 mg/kg, or approximately 5% of the acute LD_{50}, of succimer was administered subcutaneously to animals. Despite this, some authorities strongly recommend against the use of succimer in pregnancy.

COMBINED CHELATION THERAPY

Succimer can be combined with $CaNa_2EDTA$ to take advantage of the ability of succimer to remove lead from soft tissues, including the brain, while capi-

talizing on the ability of $CaNa_2EDTA$ to mobilize lead from bone. A number of animal models found the combination to be superior in enhancing the elimination of lead, reducing tissue concentrations of lead, and in reversing some lead-induced biochemical abnormalities. A retrospective review comparing BAL plus $CaNa_2EDTA$ to succimer plus $CaNa_2EDTA$ in children with blood lead levels >45 μg/mL, demonstrated a similar reduction in blood lead concentrations.

DOSING

Succimer (Chemet) is available as 100-mg bead-filled capsules. For patients who cannot swallow the capsule whole, the capsule can be separated immediately prior to use and sprinkled into a small amount of juice or on apple sauce, ice cream, or soft food, or put on a spoon and followed by a fruit drink. The dosage for lead poisoning is 350 mg/m^2 in children 3 times a day for 5 days followed by 350 mg/m^2 twice a day for 14 days. In adults, the dosage is 10 mg/kg in the same regimen as above. Using 10 mg/kg in children rather than dosing based on body surface area, as was done during the premarketing trials, may result in patient underdosing. Although not well studied, the same doses are typically used when succimer is given for metals other than lead.

DMPS is an investigational metal chelator which, like succimer, is a water-soluble analog of BAL. DMPS is associated with an increase in the urinary excretion of copper and the development of Stevens-Johnson syndrome. More research needs to be done to determine whether DMPS is more advantageous than succimer given its potential for increased toxicity.

Edetate Calcium Disodium ($CaNa_2EDTA$)

CHEMISTRY

Edetate calcium disodium ($CaNa_2EDTA$) belongs to the family of polyaminocarboxylic acids. Although it is capable of chelating many metals, its current use is almost exclusively in the management of lead poisoning. When $CaNa_2EDTA$ chelates lead, the calcium is displaced by lead, forming a stable-ring compound.

PHARMACOKINETICS

$CaNa_2EDTA$ has a small volume of distribution (0.05–0.23 L/kg) that approximates the extracellular fluid compartment. It penetrates erythrocytes poorly, and less than 5% gains access to the spinal fluid. The half-life is about 20–60 minutes and renal elimination approximates the glomerular filtration rate. As a result, 50% of a given dose of $CaNa_2EDTA$ is excreted in the urine in 1 hour and more than 95% is excreted in 24 hours. Following $CaNa_2EDTA$ administration, urinary lead excretion is increased 20–50-fold, in the form of a stable, soluble, nonionized compound.

LEAD

In animals, although $CaNa_2EDTA$ decreases tissue lead stores, it may transiently increase brain lead concentrations. Further doses are then able to enhance lead elimination, reduce blood lead concentrations, and subsequently reduce brain lead concentrations. This phenomenon may explain why some human case reports demonstrate worsening lead encephalopathy when $CaNa_2EDTA$ is used without antecedent initiation of dimercaprol (BAL) therapy.

In humans, $CaNa_2EDTA$ reduces blood lead concentrations, enhances renal excretion of lead, and reverses the effects of lead on hemoglobin synthesis. Blood lead concentrations rebound considerably days to weeks following the cessation of $CaNa_2EDTA$, as is the case after terminating other chelators. Although $CaNa_2EDTA$ has been used clinically since the 1970s, no rigorous clinical studies have ever been performed to evaluate whether $CaNa_2EDTA$ is capable of reversing the neurobehavioral effects of lead.

$CaNa_2EDTA$ MOBILIZATION TEST

The $CaNa_2EDTA$ mobilization test was once widely recommend as a diagnostic aid for assessing the potential benefits of chelation therapy. Currently, it is considered obsolete and is no longer recommended.

ADVERSE EFFECTS AND SAFETY ISSUES

The principal toxicity of $CaNa_2EDTA$ is related to the metal chelated. When $CaNa_2EDTA$ is given to patients with lead poisoning, renal toxicity results from the release of lead in the kidneys during excretion. Because lead toxicity causes renal damage independent of chelation, it is important to monitor renal function closely during $CaNa_2EDTA$ administration and to adjust the dose and schedule appropriately. Nephrotoxicity may be minimized by limit-

ing the total daily dose of $CaNa_2EDTA$ to 1 g in children or 2 g in adults, although doses may need to be higher to treat lead encephalopathy. Continuous infusion seems to increase efficacy and decrease toxicity when compared to intermittent dosing.

Because the administration of disodium EDTA (Na_2EDTA) can lead to life-threatening hypocalcemia, $CaNa_2EDTA$ has become the preparation of choice and hypocalcemia is no longer a clinical concern. Other adverse effects of $CaNa_2EDTA$, most of which are uncommon, include malaise, fatigue, thirst, chills, fever, myalgia, dermatitis, headache, anorexia, urinary frequency and urgency, sneezing, nasal congestion, lacrimation, glycosuria, anemia, transient hypotension, increased prothrombin time, and inverted T waves. Mild increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (usually reversible) and decreases in alkaline phosphatase are frequently reported. Depletion of endogenous metals, particularly zinc, iron, and manganese, can result from chronic therapy.

The safety of $CaNa_2EDTA$ has not been established in pregnancy, and a risk-to-benefit analysis must be made if its use is considered.

DOSING AND ADMINISTRATION

The dose of $CaNa_2EDTA$ is determined by the patient's body surface area or weight (up to a maximum dose) and the severity of the poisoning and renal function. For patients with lead encephalopathy, the dose of $CaNa_2EDTA$ is 1500 $mg/m^2/d$ by continuous IV infusion starting 4 hours *after* the first dose of dimercaprol and after an adequate urine flow is established. Concurrent dimercaprol and $CaNa_2EDTA$ therapies are administered for 5 days, followed by a rest period of at least 2–4 days, which permits lead redistribution. Dosage adjustments limiting the daily dose to 50 mg/kg (about 1000 mg/m^2) are necessary when $CaNa_2EDTA$ is used in patients with renal dysfunction. A blood lead concentration should be measured 1 hour after the $CaNa_2EDTA$ infusion is discontinued to avoid falsely elevated blood lead concentration determinations.

In symptomatic children without manifestations of lead encephalopathy, the dose of $CaNa_2EDTA$ is 1000 $mg/m^2/d$ in addition to dimercaprol at 50 mg/m^2 every 4 hours. Succimer is replacing $CaNa_2EDTA$ as the chelator of choice in lead-poisoned children without encephalopathy.

Because of the pain of IM administration, $CaNa_2EDTA$ is usually administered by continuous IV infusion over 24 hours in 5% dextrose or 0.9% NaCl solution. Concentrations greater than 0.5% may lead to thrombophlebitis and should be avoided. Careful attention to total fluid requirements in children and patients who have or who are at risk for lead encephalopathy is paramount, as rapid intravenous infusions may increase intracranial pressure and cerebral edema. If $CaNa_2EDTA$ is to be administered IM to avoid the use of an IV and fluid overload, then procaine is added to the $CaNa_2EDTA$ in a dose sufficient to produce a final concentration of 0.5%. This can be accomplished by mixing 1 mL of a 1% procaine solution for each mL of chelator. The procaine minimizes pain at the injection site.

COMBINATION THERAPY WITH SUCCIMER

The combination of $CaNa_2EDTA$ with succimer appears more potent than either individual drug in promoting urine and fecal lead excretion, and in decreasing blood and liver lead concentrations. However, this approach may increase nephrotoxicity and zinc depletion.

AVAILABILITY

Edetate calcium disodium EDTA is available as calcium disodium Versenate in 5 mL ampules containing 200 mg of $CaNa_2EDTA$ per milliliter (1 g per ampule). Disodium edetate (sodium EDTA) should not be considered an alternative to $CaNa_2EDTA$ because of the risk of life-threatening hypocalcemia when using sodium EDTA.

92 Mercury

HISTORY AND EPIDEMIOLOGY

The toxicologic manifestations of mercury are well known as a result of thousands of years of medicinal applications, industrial use, and environmental disasters. Mercury occurs naturally in small amounts as the elemental silver-colored liquid (quicksilver); as inorganic salts such as mercuric sulfide (cinnabar), mercurous chloride (calomel), mercuric chloride (corrosive sublimate), and mercuric oxide; and as organic compounds (methylmercury and dimethylmercury).

In the 1800s, the United States witnessed an epidemic of "hatters' shakes" in hat industry workers. In the early 1900s, acrodynia, or "pink disease," was described in children who received calomel for ascariasis or teething discomfort. In the 1940s, the Minamata Bay event occurred when methylmercury was dumped in the sea and poisoned the inhabitants of the local fishing community. The largest outbreak of methylmercury poisoning to date occurred in Iraq in late 1971 when grain treated with a fungicide was baked into bread. Approximately 6530 hospital admissions and more than 400 deaths resulted.

FORMS OF MERCURY AND KINETICS

The three important classes of mercury compounds (elemental, inorganic, and organic) differ with respect to toxicodynamics and toxicokinetics (Table 92–1). In addition, each class produces somewhat distinct clinical patterns of poisoning. Within each class, the clinical manifestations are modulated by route of exposure, rate of exposure, distribution and biotransformation within the body, and relative accumulation or elimination of mercury by the target organ systems.

Absorption

Elemental Mercury

Elemental mercury (Hg^0) is absorbed primarily via inhalation of vapor, although slow absorption following aspiration, subcutaneous deposition, and direct intravenous embolization is reported. However, as elemental mercury is negligibly absorbed from a normally functioning gut, it is usually considered nontoxic when ingested. Abnormal gastrointestinal (GI) motility prolongs mucosal exposure to elemental mercury and increases subsequent ionization to more readily absorbed forms.

Inorganic Mercury Salts

The principal route of absorption for inorganic mercury salts is the GI tract. Inorganic mercury salts are also absorbed across skin and mucous membranes, as evidenced by urinary excretion of mercury following the dermal application of mercurial ointments and powders containing HgCl.

Organic Mercury Compounds

As in the case of inorganic mercury salts, organic mercury compounds are primarily absorbed from the GI tract. Although both dermal and inhalational ab-

TABLE 92–1. Differential Characteristics of Mercury Exposure

	Elemental	Inorganic (Salt)	Organic (Alkyl)
Primary route of exposure	Inhalation	Oral	Oral
Primary tissue distribution	CNS, kidney	Kidney	CNS, kidney, liver
Clearance	Renal, GI	Renal, GI	Methyl: GI Aryl: renal, GI
Clinical effects			
CNS	Tremor	Tremor, erethism	Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary	+ + +	—	—
Gastrointestinal	+	+ + + (caustic)	+
Renal	+	+ + + (ATN)	+
Acrodynia	+	+ +	—
Therapy	BAL, succimer	BAL, succimer	Succimer (early)

+ findings present; + + + very consequential findings present.

sorption of organic mercury compounds are reported, precise quantitation and exclusion of concomitant absorption by ingestion are difficult to determine.

Distribution and Biotransformation

Following absorption, mercury distributes widely to all tissues, but predominantly to the kidneys, liver, spleen, and central nervous system (CNS). The initial distributive pattern into nervous tissue of elemental and organic mercury differs from that of the inorganic salts because of their greater lipid solubility.

Elemental Mercury

Although peak concentrations are delayed in the CNS, significant accumulation occurs following an acute, intense exposure to elemental mercury vapor. Conversion of elemental mercury to the charged mercuric cation within the CNS favors retention and local accumulation of the metal.

Inorganic Mercury Salts

The greatest concentration of mercuric ions is found in the kidneys, particularly within the renal tubules. Penetration of the blood–brain barrier is poor because of low lipid solubility, but slow elimination and prolonged exposure contribute to consequential CNS accumulation.

Organic Mercury Compounds

Once absorbed, aryl and long-chain alkyl mercury compounds differ from the short-chain organic mercury compounds (ie, methylmercury). The former possess a labile carbon-mercury bond, which is subsequently cleaved, releasing the inorganic mercuric ion. Thus, the distribution pattern and toxicologic manifestations produced by the aryl and long-chain alkyl compounds are comparable to those of the inorganic mercury salts, but the organification facilitates absorption and reduces the caustic effects. In contrast, short-chain

alkyl mercury compounds possess relatively stable carbon–mercury bonds that survive the absorptive phase. Because it is lipophilic, methylmercury readily distributes across all tissues, including blood–brain barrier and placenta. Methylmercury also concentrates in red blood cells (RBCs) to a much greater degree than do mercuric ions.

Elimination

Elemental Mercury/Inorganic Mercury Salts

Mercuric ions are excreted through the kidney by both glomerular filtration and tubular secretion, and in the GI tract by transfer across mesenteric vessels into feces. The total-body half-life of elemental mercury and inorganic mercury salts is estimated at approximately 30–60 days.

Organic Mercury Compounds

The elimination of short-chain alkyl mercury compounds is predominantly fecal. Enterohepatic recirculation contributes to its somewhat longer half-life of about 70 days. Less than 10% of methylmercury is excreted in urine and feces as the mercuric cation.

PATHOPHYSIOLOGY

Toxicity arises largely from covalent binding to sulfur, replacing the hydrogen ion in the body's ubiquitous sulfhydryl groups. This results in widespread dysfunction of enzymes, transport mechanisms, membranes, and structural proteins. Necrosis of the gastrointestinal mucosa and proximal renal tubules, which occurs shortly after mercury salt poisoning, is thought to result from direct oxidative effect of mercuric ions. An immune mechanism is attributed to the membranous glomerulonephritis and acrodynia associated with the use of mercurial ointments. Neuronal cytotoxicity of methylmercury may result in part from muscarinic receptor-mediated calcium release from smooth endoplasmic reticulum of cerebellar granule cells. Animal evidence suggests that methylmercury triggers reactive oxygen species and inhibits astrocyte uptake of cysteine, the rate-limiting step in the production of glutathione, a major antioxidant.

CLINICAL SYNDROMES

Elemental Mercury

Symptoms of *acute elemental mercury inhalation* occur within hours of exposure and consist of cough, chills, fever, and shortness of breath. Gastrointestinal complaints include nausea, vomiting, and diarrhea, accompanied by a metallic taste, dysphagia, salivation, weakness, headaches, and visual disturbances. Chest radiography during the acute phase may reveal interstitial pneumonitis and both patchy atelectasis and emphysema. Symptoms may resolve or progress to acute lung injury, respiratory failure, and death.

Subacute inorganic mercury poisoning manifested by tremor, renal dysfunction, and gingivostomatitis may also occur during the acute phase. Massive endobronchial hemorrhage followed by death has occurred secondary to direct *aspiration of metallic mercury* into the tracheobronchial tree. There is no evidence to support the development of clinically significant disease from dental amalgams.

Unusual cases of chronic toxicity have resulted from intentional *subcutaneous or intravenous injection of elemental mercury* (Fig. 92–1).

Inorganic Mercury Salts

Acute *ingestion of mercuric salts* produces a characteristic severe irritant to outwardly caustic gastroenteritis. Immediately following oropharyngeal pain, nausea, vomiting, and diarrhea develop, which are followed by abdominal pain, hematemesis, and hematochezia. The lethal dose of mercuric chloride has been estimated at 30–50 mg/kg. Renal dysfunction follows and complete renal failure can occur.

Subacute or chronic mercury poisoning occurs after (a) inhalation, aspiration, or injection of elemental mercury; (b) ingestion or application of inorganic mercury salts; or (c) ingestion of aryl or long-chain alkyl mercury compounds. Slow in vivo oxidation of elemental mercury and dissociation of the carbon-mercury bond of aryl or long-chain alkyl mercury compounds result in the production of the inorganic mercurous and mercuric ions.

The predominant manifestations of subacute or chronic mercury toxicity include gastrointestinal symptoms, neurologic abnormalities, and renal dysfunction. Gastrointestinal symptoms consist of a metallic taste and burning sensation in the mouth, loose teeth and gingivostomatitis, hypersalivation (ptyalism), and nausea. The neurologic manifestations of chronic inorganic

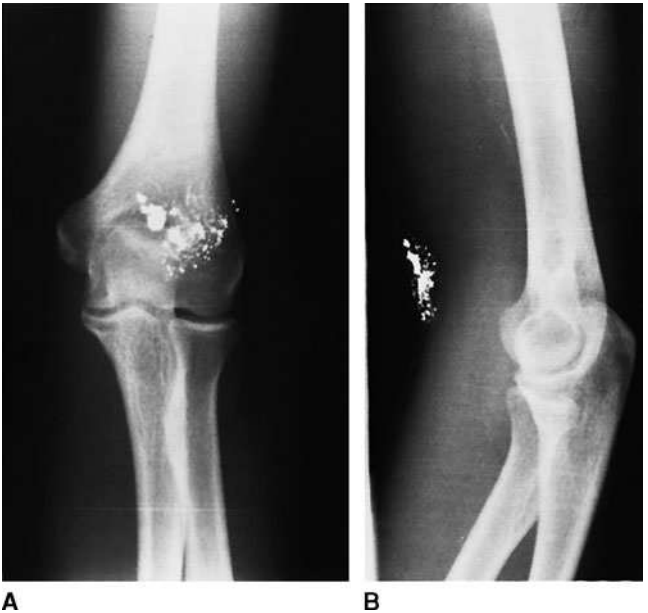

FIG. 92–1. Anteroposterior **(A)** and lateral **(B)** view of the elbow after an unsuccessful suicidal gesture involving an attempted intravenous injection of mercury in the antecubital fossa. Note extensive mercury deposition, which was partially removed by surgical intervention. *(Courtesy of Diane Sauter, MD.)*

mercurialism include tremor, as well as the syndromes of neurasthenia and erethism. Neurasthenia is a symptom complex that includes fatigue, depression, headaches, hypersensitivity to stimuli, psychosomatic complaints, weakness, and loss of concentrating ability. Erethism, derived from the Greek word *red*, describes the easy blushing and extreme shyness of the afflicted. Other symptoms of erethism include anxiety, emotional lability, irritability, insomnia, anorexia, weight loss, and delirium. The mercurial tremor is well described in numerous case reports as a central intention tremor that is abolished during sleep. In the most severe forms of mercury-associated tremor, choreoathetosis and spasmodic ballismus may be present. Other neurologic manifestations of inorganic mercurialism include a mixed sensorimotor neuropathy, ataxia, concentric constriction of visual fields ("tunnel vision") and anosmia.

Renal dysfunction ranges from asymptomatic reversible proteinuria, to nephrotic syndrome with edema and hypoproteinemia. An idiosyncratic hypersensitivity to mercury ions is thought to be responsible for acrodynia or "pink disease," which is an erythematous, edematous, and hyperkeratotic induration of the palms, soles, and face, and a pink papular rash, described as morbilliform, urticarial, vesicular, and hemorrhagic. This symptom complex also includes excessive sweating, tachycardia, irritability, anorexia, photophobia, insomnia, tremors, paresthesias, decreased deep-tendon reflexes, and weakness. The acral rash may progress to desquamation and ulceration.

Organic Mercury Compounds

In contrast to the inorganic mercurials, methylmercury produces an almost purely neurologic disease that is permanent except in the mildest of cases. Although the predominant syndrome associated with methylmercury is that of a delayed neurotoxicity, acutely, gastrointestinal symptoms, tremor, respiratory distress, and dermatitis may occur.

Characteristically, manifestations follow a latent period of weeks to months. Infants exposed prenatally to methylmercury were the most severely affected individuals in Minamata. Often born to mothers with little or no manifestation of methylmercury toxicity themselves, exposed infants exhibited decreased birth weight and muscle tone, profound developmental delay, seizure disorders, deafness, blindness, and severe spasticity. Several weeks after methylmercury-contaminated grain was ingested paresthesias involving the lips, nose, and distal extremities developed, as did headaches, fatigue, and tremor. More serious cases progressed to ataxia, dysarthria, visual field constriction, and blindness.

Dimethylmercury's extreme toxicity was demonstrated by the delayed fatal neurotoxicity that developed in a chemist who spilled dimethylmercury on her gloved hands. Progressive difficulty with speech, vision, and gait preceded her death.

LABORATORY

Demonstration of mercury in blood, urine, or tissues is necessary for confirmation of exposure. Blood should be collected into a trace-element collection tube obtained from the laboratory performing the assay. Urine should be collected for 24 hours into an acid-washed container obtained from the laboratory. Spot collections must be adjusted for creatinine concentration.

There is considerable overlap among concentrations of mercury found in the normal population, asymptomatic exposed individuals, and patients with clinical evidence of poisoning. However, concentrations less than 10 μg/L for whole

blood and 20 μg/L for urine are generally considered to reflect background exposure in nonpoisoned individuals. Following long-term exposure to elemental mercury vapor, concentrations as low as 35 μg/L for blood and 150 μg/L for urine may be associated with nonspecific symptoms of mercury poisoning. Because organic mercury is eliminated via the fecal route, urine mercury levels are not useful in methylmercury poisoning. Because mercury accumulates in hair, hair analysis has been employed as a tool for measuring mercury burden. However, as metal incorporation reflects past exposure, and hair avidly binds mercury from the environment, the reliability of this method is questionable and is not recommended.

INITIAL MANAGEMENT

After initial assessment and stabilization, the early toxicologic management of mercury poisoning includes termination of exposure by removal from vapors; washing exposed skin; gastrointestinal decontamination; supportive measures such as hydration and humidified oxygen; baseline diagnostic studies such as complete blood count, serum chemistries, arterial blood gas, radiographs, and electrocardiogram; specific analysis of blood and urine for mercury; consideration of possible coingestants; and meticulous monitoring.

Elemental Mercury

Inhalation of mercury vapors or aspiration of metallic mercury may result in life-threatening respiratory failure, and in this situation, stabilization of cardiorespiratory function is the initial priority. Postural drainage and endotracheal suction may be effective in removing aspirated metallic mercury. Parenteral deposition of subcutaneous or intramuscular mercury may be amenable to surgical excision if well localized.

Inorganic Mercury Salts

Ingestion of inorganic mercuric salts may lead to cardiovascular collapse caused by severe gastroenteritis and third-space fluid loss. Fluid resuscitation is a priority. Although gastrointestinal decontamination is particularly problematic because of their causticity and risk for perforating injury, unless there is high suspicion for penetrating gastrointestinal mucosal injury, removal of mercury from absorptive surfaces should take priority over endoscopic evaluation. The prominence of vomiting makes gastric lavage unnecessary for most patients with inorganic mercury poisoning. Because inorganic mercuric salts have substantial adsorption to activated charcoal (800 mg mercuric chloride can be absorbed to 1 g activated charcoal in vitro), administration is justified. Whole-bowel irrigation with polyethylene glycol solution may also be useful in removing residual mercury, and should be considered, following its progress with serial radiographs.

Organic Mercury Compounds

Because organic mercury exposures do not typically present as single, acute ingestions, but rather as chronic or subacute ingestion of contaminated food, gastrointestinal decontamination is generally unnecessary.

TREATMENT: CHELATION

Early chelation may minimize or prevent the widespread effects of poisoning. Hemodialysis, although ineffective at removing mercury, may be necessary

because of the acute renal failure that often follows mercuric chloride poisoning. A history of significant mercury exposure combined with the presence of typical symptoms of mercury poisoning is an appropriate indication for the institution of chelation therapy, even if laboratory confirmation is pending. Provocative chelation, in which urinary mercury excretion before and after a chelating dose is compared to determine the degree of mercury poisoning, is of dubious value.

Elemental Mercury and Inorganic Mercury Salts

For clinically significant acute inorganic mercury poisoning, dimercaprol (BAL) should be administered for 10 days in decreasing dosages of 5 mg/kg/dose every 4 hours IM for 48 hours, then 2.5 mg/kg every 6 hours for 48 hours, then 2.5 mg/kg every 12 hours for 7 days. When a patient is able to take oral medications and the gastrointestinal tract is clear, succimer at 10 mg/kg orally 3 times a day for 5 days, then twice a day for 14 days, can be substituted for BAL (see Antidotes in Brief: Dimercaprol [British Anti-Lewisite or BAL] and Antidotes in Brief: Succimer).

Organic Mercury Compounds

The neurotoxicity of methylmercury and other organic mercury compounds is resistant to treatment, and therapeutic options are less than satisfactory. BAL should not be used because animal evidence suggests that BAL may increase mercury mobilization into the brain. Although further investigation is necessary, succimer may prove to be the treatment of choice for methylmercury poisoning because of its apparently low toxicity and reported efficacy in animal trials.

93 Nickel

HISTORY AND EPIDEMIOLOGY

Nickel is a white, lustrous metal first identified in 1751. It comprises 0.008% of the crust of the earth and is found in diverse locations ranging from meteorites and soil to bodies of fresh and salt water. Nickel has been used as a component in a variety of metal alloys for more than 1700 years.

Nickel is a siderophoric material that forms naturally occurring alloys with iron, a property that has made it useful for many centuries in the production of coins, tools, and weapons. Today, most nickel is used in the production of stainless steel, a highly corrosion-resistant alloy containing 8–15% nickel by weight.

Occupational exposure to nickel and nickel-containing compounds can occur in a variety of industries, including nickel mining, refining, reclaiming, and smelting. Chemists, magnet makers, jewelry makers, oil hydrogenator workers, battery manufacturers, petroleum refinery workers, electroplaters, stainless steel and alloy workers, and welders may be at increased risk for exposure to nickel and nickel-containing compounds. Nickel carbonyl is responsible for the majority of acute occupational nickel toxicity. In contrast, the most common health issue related to nickel is the development of allergic dermatitis from jewelry and clothing. Nickel ranks behind poison ivy and poison oak as the second most common cause of allergic contact dermatitis.

TOXICOLOGY AND PHARMACOKINETICS

Diet is a source of nickel exposure for humans. Foods high in nickel include nuts, legumes, cereals, and chocolate. Nickel is not considered an essential element for human health and dietary recommendations for nickel have not been established. Concentrations of metallic nickel in drinking water in the United States are generally below 20 μg/L. Elevated levels of nickel in potable water result from leaching of nickel alloys in plumbing fixtures.

Nickel carbonyl is a highly volatile, deadly, liquid nickel compound used in nickel refining, petroleum processing, and as a chemical reagent. Its high vapor pressure and high lipid solubility lead to rapid systemic absorption through the lungs. In the air, and in the body, it decomposes into metallic nickel and carbon monoxide, and its toxicity has been compared to that of hydrogen cyanide.

Absorption

Depending on the form, nickel can enter the body through the skin, lungs, and gastrointestinal tract. Following inhalational exposure, nickel tends to accumulate in the lungs, and only 20–35% of nickel deposited in the human lung is absorbed. The remainder of the inhaled material is swallowed, expectorated, or deposited in the upper respiratory tract. Subsequent systemic absorption from the respiratory tract is dependent on the solubility of the specific nickel compound in question. Soluble nickel salts (nickel sulfate or nickel chloride) are more easily absorbed, whereas the less soluble oxides and sulfides of nickel have much lower levels of absorption.

Following ingestion, approximately 27% of the total nickel in nickel sulfate given to humans in drinking water is absorbed, whereas only approxi-

mately 1% is absorbed when given in food. Serum nickel concentrations peak from 1.5–3 hours following ingestion of nickel. Several nickel compounds are capable of penetrating the skin. However, it has not been determined if nickel is simply absorbed into the deep layers of the skin or if it actually reaches the bloodstream. Once absorbed, nickel exists in the body primarily as the divalent cation.

Distribution

In human serum, the exchangeable pool of primarily divalent nickel is bound to albumin, L-histidine, and α_2-macroglobulin. A nonexchangeable pool of nickel also exists and is tightly bound to a transport protein known as nickeloplasmin. Nickel is also concentrated in various solid organs with the highest concentrations in the lungs, followed by the thyroid, adrenals, kidneys, heart, liver, brain, spleen, and pancreas.

Elimination

Most ingested nickel is excreted in the feces; however, as more than 90% of ingested nickel does not leave the gut, most nickel found in feces represents this unabsorbed fraction rather than the elimination of previously absorbed nickel. Regardless of the route of exposure, absorbed nickel is excreted in the urine. The half-life of elimination of nickel depends on the source of exposure. Following unintentional ingestion of contaminated water, the mean serum half-life of nickel was reported to be 60 hours. This half-life decreased substantially (to 27 hours) following treatment with intravenous fluids. Prolonged elevation of serum and urine nickel concentrations result from inhalation of insoluble nickel with continued slow absorption.

CLINICAL MANIFESTATIONS

Acute

The most important source of acute, nondermatologic nickel toxicity is nickel carbonyl. Exposure to this compound is associated with pulmonary, neurologic, and hepatic dysfunction. Inhalation of nickel-containing aerosolized particles tends to affect the lungs and upper airways directly, whereas ingestion and intravenous administration may result in systemic toxicity, usually involving the neurologic system. By far the most common disorder associated with acute exposure to nickel is an allergic dermatitis.

Nickel Dermatitis

Nickel is recognized as one of the most common causes for allergic contact dermatitis. One population survey reported that 3% of males and 15% of females demonstrated evidence of allergy to nickel. Nickel dermatitis may be classified into primary and secondary types. The more common primary dermatitis presents as a typical eczematous reaction in the area of skin that is in contact with nickel. It is characterized initially by erythematous papules that may proceed to lichenification. Areas typically involved include sites of contact with nickel-containing jewelry, buttons on jeans, and nickel-containing belt buckles. The secondary form involves a more widespread dermatitis as a result of other exposures such as ingestion, transfusion, inhalation, implantation of metal medical devices, and may be regarded as a systemic contact dermatitis elicited by nickel. Secondary eruptions are typically symmetrically

distributed and may localize in the elbow flexure, on the eyelids, sides of the neck, and face, and may sometimes become widespread.

The allergic reaction caused by contact with nickel is a type IV delayed hypersensitivity immune response that typically occurs in two phases. In the first phase, sensitization occurs when nickel enters the body. The second phase occurs when the body is reexposed to nickel. The diagnosis of nickel allergy is suggested by specific historical findings (Table 93–1).

Nickel Carbonyl

Exposure to 2 ppm (14 mg/m^3) of nickel carbonyl is immediately dangerous to life or health. Symptoms may occur rapidly or be delayed. In one series of exposures, approximately 40% of patients reported symptoms within 1 hour of exposure. It is important to note, however, that symptoms were delayed for approximately 1 week in 20% of patients, and even patients with mild initial symptoms could develop severe delayed symptoms, although usually within the next 2 days. The initial manifestations include nonspecific complaints including respiratory tract irritation, chest pain, cough, and dyspnea, as well as frontal headache, dizziness, weakness, and nausea. Cases manifesting only these initial signs are categorized as mild poisoning.

Symptoms of severe acute nickel carbonyl poisoning generally develop over the course of several hours to days and may be associated with acute lung injury and interstitial pneumonitis. Myocarditis, marked by ECG abnormalties including ST-segment and T-wave changes, as well as QTc interval prolongation, occur. Neurologic symptoms include altered mental status, seizures, and extreme weakness, sometimes necessitating mechanical ventilation. A moderate leukocytosis (10,000–15,000 WBC/mm^3), nonspecific opacities on chest radiography, and elevation of aminotransferases may occur, but these tend to resolve over the course of several weeks. Deaths from nickel carbonyl exposures are typically caused by interstitial pneumonitis and cerebral edema occurring within 2 weeks of initial exposure.

Parenteral Administration

Acute parenteral toxicity from nickel-containing compounds occurred when water used in hemodialysis was heated in a nickel-plated tank. Patients developed nonspecific symptoms, including headache, nausea, and vomiting, similar to nickel carbonyl poisoning, although no respiratory complaints are reported. The effects resolve after several hours, and recovery is without sequelae.

Acute ingestions of water contaminated with nickel salts causes nausea, vomiting, diarrhea, weakness, and headache, as well as pulmonary symptoms, including cough and dyspnea, which may persist for 48 hours.

TABLE 93–1. Findings Suggestive of Nickel Dermatitis

Previous history of allergic response to jewelry
Multiple piercings
Eruptions at the site of metal contact, or flexural areas if generalized
Eruptions following placement of orthodontic appliances containing high concentrations of nickel (unusual)
Seasonal dermatitis in warm months (increased metal–skin contact and increased sweating)

Chronic Nickel Exposure

Chronic inhalational exposure to nickel is associated with injury as well as specific histologic changes in the nasopharynx and upper respiratory tract, including atrophy of the olfactory epithelium rhinitis, sinusitis, nasal polyps, and septal damage. More distal pulmonary effects may include asthma and pulmonary fibrosis.

DIAGNOSTIC TESTING

Even though nickel is widely distributed to many body fluids and tissues, urine and blood are the most commonly analyzed samples. Urine and blood nickel concentrations primarily reflect exposure in the past 2 days. The average nickel concentration in serum is 0.3 μg/L, whereas the value in urine ranges from 1–3 μg/L. Concentrations among workers occupationally exposed to nickel may be substantially higher and serum concentrations greater than 8 μg/L are indicative of excessive exposure.

TREATMENT

The first step in treatment of nickel-related medical problems is eliminating the exposure. This includes detection and removal of the source. In the case of acute exposures to nickel carbonyl, removal of clothing to prevent continued exposure and thorough skin decontamination may be necessary.

Symptomatic treatment for pulmonary symptoms can include the administration of supplemental oxygen for hypoxia. The use of bronchodilators and corticosteroids also may be necessary for the treatment of concomitant bronchospasm. Mechanical ventilation is required in the most severe cases.

The administration of intravenous fluids to promote diuresis reduces the half-life of orally ingested nickel chloride by approximately 50%. Hemodialysis does not effectively remove nickel from the serum.

Chelation

Because there are no controlled human trials, specific recommendations for the use of chelation to treat nickel toxicity are supported only by extrapolation from animal studies and case reports. Some protection can be demonstrated with dimercaprol (BAL) and D-penicillamine, whereas calcium ethylenediaminetetraacetic acid (CaEDTA) has no protective effect. Although BAL has been used in the past, the most recent literature has focused on the use of diethyldithiocarbamate (DDC) (Chaps. 77 and 96).

Patients with suspected severe poisonings are typically given the first gram of DDC in divided oral doses. When less severe exposures are suspected, treatment decisions are based on the urinary nickel concentration. At concentrations less than 10 μg/dL, no initial therapy is given, as delayed symptoms are unlikely to develop. At concentrations between 10 and 50 μg/dL an oral regimen consisting of 1 g DDC initially, 0.8 g at 4 hours, 0.6 g at 8 hours, and 0.4 g at 16 hours is used. DDC is continued at a dose of 0.4 g every 8 hours until there is symptomatic improvement and urine nickel concentration is normal. Severe exposures with urinary nickel concentrations of >50 μg/dL may be treated using the same regimen, although these patients frequently require closer monitoring. Critically ill patients are given parenteral DDC starting at a dose of 12.5 mg/kg. Although typically well tolerated, DDC is capable of inducing a disulfiram reaction (Chap. 77) if taken with alcohol, and

there are concerns that DDC should be avoided as it may exacerbate concurrent cadmium exposure.

Disulfiram is metabolized into 2 molecules of DDC. Given that DDC is not pharmaceutically available in the United States, there is some interest in the use of disulfiram as an antidote for nickel carbonyl. Although case reports describe successful treatment of nickel carbonyl toxicity with disulfiram, concern exists because of animal studies showing that disulfiram increased nickel concentration in brain tissue. One treatment regimen was 750 mg PO every 8 hours for 24 hours followed by 250 mg every 8 hours. Consequently, DDC is considered the treatment of choice for nickel toxicity where available. It is recommended that the regional poison control center be contacted if necessary to assist with treatment decisions.

Contact dermatitis from nickel is treated with standard measures, including avoidance, topical steroids, and antihistamines.

94 Selenium

Selenium was discovered in 1817. It has unusual light-sensitive electrical conductive properties, leading to its use throughout industry. It is both an essential component of the human diet, as well as a potentially deadly poison.

HISTORY AND EPIDEMIOLOGY

In the 1970s selenium was found to be an essential cofactor of the enzyme glutathione peroxidase. Deficiency occurs below 20 μg/d. Keshan disease, an endemic cardiomyopathy associated with multifocal myonecrosis, periacinar pancreatic fibrosis, and mitochondrial disruption, was described in patients who consumed a selenium-poor diet over years. The recommended daily allowance (RDA) for selenium was established in 1980 in the United States as 55 μg/d. Dietary selenium is easily obtained through meats, grains, and cereals; Brazil nuts, grown in the foothills of the highly seleniferous Andes Mountains, contain the highest concentration measured in food.

Chronic selenium toxicity, or selenosis, has also occurred throughout history. Humans in seleniferous areas of China and Venezuela develop dermatitis, hair loss, and nail changes at an intake more than 100 times the RDA.

Selenium sulfide is the active ingredient in many antidandruff shampoos. Gun-bluing solution, used to care for the exterior surface of firearms, is composed of selenious acid, as well as other compounds, such as cupric sulfate in hydrochloric acid, nitric acid, copper nitrate, and methanol. Table 94–1 lists industrial uses of selenium compounds.

CHEMICAL PRINCIPLES

Selenium is a nonmetal element of group VIA of the periodic table, which also contains oxygen, sulfur, and tellurium. It is found in abundance throughout the earth's crust, usually as a metal selenide in sulfide ores such as marcasite, arsenopyrite, and chalcopyrite. Selenium exists in elemental, organic and inorganic forms, with important oxidation states of 0 (elemental), +2 (selenide [Se^{2+}]), +4 (selenite [SeO_3^{2+}]), and +6 (selenate [SeO_4^{2+}]). Solubility in water generally increases with oxidation state, so elemental selenium and metal selenides are insoluble, whereas alkali selenites and selenates are highly water soluble. In general, toxicity from elemental selenium is rare and only occurs from long-term exposure. The organic alkyl compounds (dimethylselenide, trimethylselenide) are the next least toxic; in fact, they are byproducts of endogenous selenium detoxification (methylation). Selenious acid (H_2SeO_3) is the most toxic form of selenium.

PHARMACOLOGY AND PATHOPHYSIOLOGY

There are three categories of selenium normally found in the body. First, selenium-specific proteins, or selenoproteins, contain selenocysteine residues and play specific roles, primarily in oxidation-reduction (redox) physiology. Second, a number of nonspecific proteins contain selenium, such as albumin and selenomethionine, in which selenium appears to have no specific role, but which may represent a storage form of selenium. Third, selenium has several

TABLE 94–1. Selenium Compounds and Their Uses

Chemical Formula	Name	Uses
Se	Selenium, elemental	Photography, catalyst, xerography
SeS_2	Selenium sulfide	Antidandruff shampoo
SeO_2	Selenium dioxide	Catalyst, photography, xerography, glass decolorizer, vulcanization of rubber
$SeOCl_2$	Selenium oxychloride	Solvent, plasticizer
SeF_6	Selenium hexafluoride	Gaseous electrical insulator
H_2SeO_3	Selenious acid	Gun bluing solution
H_2Se	Hydrogen selenide, selenium hydride	—
Na_2SeO_3	Sodium selenite	Glass and porcelain manufacture
Na_2SeO_4	Sodium selenate	Insecticide

inorganic forms throughout the body, such as selenate, alkyl selenides, and elemental selenium (Se^o).

In selenium deficiency, glutathione peroxidase activity is decreased, and reduced glutathione (GSH) and GSH-S transferases are increased. In animals, selenium deficiency increases susceptibility to substances detoxified by GSH-S transferase, such as acetaminophen and aflatoxin B, and potentiates toxicity from prooxidants such as nitrofurantoin, diquat, and paraquat.

Less is known about the biochemical mechanism of selenium toxicity, and what is known is not from overdose data, but from in vitro studies. Paradoxically, excess selenium causes oxidative stress, presumably as a result of prooxidant tendencies of selenide (RSe) anions. In addition, the replacement of selenium for sulfur in enzymes of cellular respiration may cause mitochondrial disruption, and interference with protein synthesis. Selenium's integumentary effects are also most likely caused by interpolation of selenium into disulfide bridges of structural proteins such as keratin.

PHARMACOKINETICS AND TOXICOKINETICS

Gastrointestinal absorption varies with the species of selenium, and human data are limited. Elemental selenium is the least bioavailable (up to 50%); inorganic selenite and selenate salts (75%); selenious acid is quite well absorbed in the lungs and gastrointestinal tract, approximately 85% in animal studies. Organic selenium compounds are the best absorbed at approximately 90% as determined by isotope tracers in human volunteer studies. Dermal absorption appears to be limited and selenium disulfide shampoos are not systemically absorbed at recommended usage.

The toxic dose of selenium varies widely between selenium compounds, and parallels gastrointestinal bioavailability. Elemental selenium has no reported adverse effects in acute overdose, although long-term exposure can be harmful. The selenium salts, particularly selenite, are more acutely toxic, as is selenium oxide (SeO_2), through its conversion to selenious acid in the presence of water. Selenious acid may be lethal, from as little as a tablespoon of 4% solution in children.

The metabolic fate of selenium centers on the selenide anion, which has one of three final fates: (a) incorporation into selenoproteins such as glutathione peroxidase and triiodothyronine; (b) binding by nonspecific plasma

proteins such as albumin or globulins; or (c) hepatic methylation into nontoxic excretable metabolites. Trimethylselenide is the primary metabolite and is excreted by the kidneys, the major elimination pathway for selenium. Some fecal elimination also occurs.

CLINICAL MANIFESTATIONS

Acute Overdose

Dermal exposure to selenium dioxide, which is converted to selenious acid, and to selenium oxychloride, causes painful caustic burns through generation of hydrochloric acid. Excruciating pain may result from accumulation under fingernails. Selenious acid can also produce a pustular and ulcerative caustic burn.

Corneal burns with severe pain, lacrimation, and conjunctival edema are reported after exposure to selenium dioxide.

Inhalational Exposure

When inhaled, all selenium compounds are potential respiratory irritants. In general, inhaled elemental selenium dusts are less systemically toxic than those compounds that are converted to selenious acid. Acute exposure to high concentrations of hydrogen selenide gas produces throat and eye pain, rhinorrhea, wheezing, and pneumomediastinum, with residual restrictive and obstructive disease. In contrast, selenium dioxide and selenium oxide fumes form selenious acid in the presence of water in the respiratory tract. Initial symptoms include bronchospasm with upper respiratory irritation and burning. Hypotension, tachycardia, and tachypnea may occur transiently. Chemical pneumonitis with fever, chills, headache, vomiting, and diarrhea can develop later. Selenium hexafluoride is a caustic gas used in industrial settings as an electrical insulator. Its caustic properties are derived from its conversion, in the presence of water, to elemental selenium and hydrofluoric acid. Signs and symptoms are consistent with hydrofluoric acid (HF) exposure (Chap. 101).

Oral Exposure

There are no reported cases of acute overdose with elemental selenium. Following ingestion of selenium salts and selenium oxides, gastrointestinal symptoms predominate, and there is usually a good outcome. Ingestion of even small quantities of selenious acid, however, is almost invariably fatal. Selenium oxide and dioxide are also highly toxic via the oral route, presumably because of their conversion to selenious acid.

More severely poisoned patients develop weakness, elevation in creatine phosphokinase (CPK) concentrations, and renal insufficiency as a result of direct tissue injury, myoglobinuria, and hemolysis. Caustic esophageal and gastric burns, myocardial and mesenteric infarction, and metabolic acidosis all contribute to poor outcome in these patients. Multisystem organ failure often results, with the acute respiratory distress syndrome, cerebral edema, and death.

Chronic

Many descriptions of chronic selenium toxicity, or selenosis, come from inhabitants of the Hubei province of China from 1961–1964, the majority of whom developed clinical signs after an estimated average consumption of 5

mg of selenium per day (but as little as 910 μg/d). Selenosis is similar to arsenic toxicity, with its most consistent manifestations being nail and hair abnormalities. The hair becomes very brittle, breaking off easily at the scalp, with regrowth of discolored hair, and the development of an intensely pruritic scalp rash. The nails are also brittle with white or red ridges which can be either transverse or longitudinal; the thumb is usually involved first, and paronychia can develop. The skin becomes erythematous, swollen, and blistered, slow to heal, and with a persistent red discoloration. An increased in dental caries can occur. Neurologic manifestations include hyperreflexia, peripheral paresthesias, anesthesia, and hemiplegia. Selenosis also may occur as a result of occupational exposure and overzealous dietary supplement use.

DIAGNOSTIC TESTING

Over time, selenium is incorporated into blood and erythrocyte proteins. Consequently, whole-blood and erythrocyte selenium concentrations are more useful to quantify chronic exposure, whereas plasma and serum concentrations change rapidly in relation to selenium intake and are better measures following acute exposure. In general, a plasma concentration greater than 1 mg/L is associated with mild toxicity, and greater than 2 mg/L, with serious toxicity. Urine concentrations reflect very recent exposure, as urinary excretion of selenium is maximum within the first 4 hours. In general, a normal urinary concentration is less than 0.03 mg/L. The usefulness of hair selenium is limited in countries such as the United States where the use of selenium sulfide shampoos is widespread.

Other ancillary tests to assess selenium toxicity include ECG, thyroid function, platelet counts, aminotransferases, creatinine, and serum creatine kinase.

MANAGEMENT

Treating painful skin or nail bed burns or ocular pain with 10% sodium thiosulfate solution or ointment may provide relief of symptoms; this may be a consequence of a reduction in the ratio of selenium dioxide to elemental selenium. Workers exposed to selenium hexafluoride gas can be treated with calcium gluconate gel to affected areas. This is the same treatment as for hydrofluoric acid exposures (Chap. 101).

As with any toxic exposure, prompt removal from the source is required, if possible. Patients with dermal exposure should be irrigated immediately. There are limited data to support the use of aggressive gastrointestinal decontamination following the ingestion of most selenium substances as there is little expected acute toxicity. However, in compounds associated with systemic toxicity, such as the selenite salts, decontamination with orogastric lavage or activated charcoal might be warranted. Special consideration should be given to the ingestion of selenious acid, which acts both as a caustic with attendant decontamination difficulties, and a serious systemic poison. The judicious use of nasogastric lavage may be indicated based on time since ingestion, amount ingested, presence or absence of spontaneous emesis, and the clinical condition of the patient.

There are no proven antidotes for selenium toxicity. Animal studies and scant human data suggest that chelation with dimercaprol (BAL), edetate calcium disodium ($CaNa_2EDTA$), or succimer forms nephrotoxic complexes with selenium, does not speed clinical recovery, and may, in fact, worsen tox-

icity. Extracorporeal removal techniques such as hemodialysis or hemofiltration decrease selenium concentrations in patients undergoing the procedure regularly for renal failure. However, because of extensive protein binding, this benefit may be only minor and only relevant to patients undergoing frequent dialysis.

Supportive care is the mainstay of therapy in selenium poisoning. In particular, patients with selenious acid toxicity will require intensive monitoring and multisystem support to survive.

95 Silver

Silver is a precious metal that has been used for thousands of years as coinage, a financial standard, a chemical catalyst, an electrical conductor, and a medicinal ingredient and adjunct. Silver poisoning is rare and results from occupational exposure or self-administration of silver-containing products for unproven medicinal purposes.

Colloidal silver proteins (CSPs), a suspension of finely divided metallic silver made from mixing silver nitrate, sodium hydroxide, and gelatin, was used in oral medications in the late 19th and early 20th centuries to treat a variety of ailments, including syphilis, epilepsy, and nasal allergies. While banned from routine administration by intravenous, intramuscular, and oral routes in the United States, silver salts are approved for use in topical medications, primarily as a caustic to stop bleeding and as a key component of burn care. Silver sulfadiazine added to burn dressings kills bacteria and increases the rate of reepithelialization across partial-thickness wounds. Central venous catheters impregnated with silver sulfadiazine and silver-impregnated Foley catheters are used to lower infection rates.

EPIDEMIOLOGY AND PHARMACOLOGY

A number of occupations expose humans to varying amounts of silver on a daily basis. The estimated oral intake of silver for humans ranges from 10–88 μg/d. Silver is excreted in the bile and eliminated in the feces (30–80 μg/d) and urine (10 μg/d). The elimination half-life varies with route of administration from 24 hours with oral exposure to 2.4 days following intravenous administration. Although one human study on a single subject showed 18% of a single dose of orally administered silver was retained after 30 weeks, animal studies show little silver absorption along the GI tract and 90% of ingested silver as excreted within 2 days.

Metallic silver binds to reactive groups of proteins (sulfhydryl, amine, carboxyl, phosphate, and imidazole) to provoke protein denaturation and precipitation. Its antimicrobial effects are thought to result from inhibition of fungal DNAse and complexation with bacterial DNA.

CLINICAL MANIFESTATIONS

When used as intended and under average exposure conditions, silver is generally not considered to be toxic. In large enough quantities, however, silver manifests cardiovascular, hepatic, and hematopoietic toxicity. Acutely, intravenous administration of 50 mg or more of silver is fatal, leading to acute lung injury, hemorrhage, and necrosis of bone marrow, liver, and kidneys. With chronic administration, limited animal and human data suggest a rare potential to cause cardiac hypertrophy, hepatic necrosis, marrow depression with subsequent leukopenia or aplastic anemia, acute tubular necrosis, and neurologic injury. The most classic manifestation, however, is argyria.

Argyria

Argyria is described as a permanent bluish-gray discoloration of skin resulting from silver deposition throughout the integument. Commonly, argyria is a re-

sult of mechanical impregnation of skin by silver particles in workers involved in silver mining and manufacturing, coating of metallic films on glass and china, manufacture of electroplating solutions and photographic processing, preparation of artificial pearls, or simple cutting and polishing of silver. Local routes of silver absorption may be through the conjunctiva or oral mucous membranes after prolonged topical treatment with silver salts or short-contact acupuncture. Of greater concern, however, is that colloidal silver protein ingestion for "health supplementation" leads to body burdens of silver that can lead to argyria.

Surprisingly, although no pathologic changes or inflammatory reactions are seen at a histologic level from silver deposition or impregnation, increased production of melanin is induced. Thus, patients with argyria commonly manifest increased pigmentation over sun-exposed skin. The proposed mechanism for this process is that silver-complexed proteins are reduced to their elemental form via photoactivation, similar to photographic image development. Silver plus light then further stimulates melanogenesis, increasing additional melanin in light-exposed areas.

Argyria progresses in stages beginning with characteristic gray-brown staining of gingiva, then moving to hyperpigmentation and discoloration in sun-exposed areas. Later, sclerae, nail beds and mucous membranes become hyperpigmented and on autopsy viscera have been noted to be blue. Confirmation of the diagnosis of argyria is through skin biopsy and hematoxylin and eosin staining.

Argyria occurs at exposure concentrations much lower than those associated with acutely toxic effects of silver; the degree of discoloration is directly proportional to the amount of silver absorbed or ingested. Although 8 g of silver accumulation is typically necessary before argyria is noted, the lowest known dose of silver resulting in argyria was 1 g of metallic silver administered as 4 g of silver arsphenamine intravenously.

DIAGNOSTIC TESTING

Serum silver concentrations can confirm exposure, normal values are reported as ≤ 1 μg/L. Patients with argyria have had serum concentrations of silver as high as 500 μg/L.

TREATMENT

Chelators such as British anti-Lewisite and D-penicillamine are ineffective in treating both toxicity and argyria. Hydroquinone 5% might reduce the number of silver granules in the upper dermis and around sweat glands, as well as diminish the number of melanocytes. Sunscreens and opaque cosmetics are used to prevent further pigmentation darkening from sun exposure.

96 Thallium

HISTORY AND EPIDEMIOLOGY

Thallium, atomic number 81, is used in alloys as an anticorrosive, in optical lenses to increase the refractive index, in artist's paints, in lamps to improve tungsten filaments, in imitation jewelry, as a catalyst, and in fireworks. In the early 1900s, thallium salts were used medicinally to treat syphilis, gonorrhea, tuberculosis, and ringworm of the scalp, and as a depilatory. Because many cases of severe thallium poisoning resulted, this treatment was rapidly abandoned. However, because thallium sulfate is odorless and tasteless, it was used until 1965 as a household rodenticide in the United States. Commercial use of thallium rodenticides was banned in the United States in 1975. Unfortunately, life-threatening unintentional poisoning continues in countries where thallium rodenticides are still used. Additional cases of thallium poisoning are reported as a result of use as a homicidal agent and through contamination of herbal products and illicit drugs, such as heroin and cocaine.

TOXICOKINETICS

Exposures usually occur via one of three routes: *inhalation* of dust, *ingestion*, and *absorption* through intact skin. Thallium is rapidly absorbed following all routes of exposure. The volume of distribution for thallium is very large: 3.6 L/kg. Although thallium is found in all organs, it is distributed unevenly, with higher concentrations found in the large and small intestine, liver, kidney, heart, brain, and muscles. The elimination half-life is 1.7 days in humans. Thallium is excreted primarily via the feces (51.4%) and the urine (26.4%). It is glomerularly filtered, and approximately 50% is reabsorbed in the tubules. It is also secreted into the tubular lumen in a manner similar to potassium.

PATHOPHYSIOLOGY

Thallium behaves biologically like potassium because of their similar ionic radii (0.147 nm for thallium and 0.133 nm for potassium). Because cell membranes cannot differentiate between thallium and potassium ions, thallous ions accumulate in areas with high potassium concentrations such as central and peripheral nervous, hepatic, and muscular tissues. Thallium replaces potassium in the activation of potassium-dependent enzymes. In low concentrations, thallium stimulates these enzyme systems, but in high concentrations, it inhibits them. Thallium also inhibits pyruvate kinase, succinate dehydrogenase, $Na^{-}K^{+}$ ATPase, and impairs depolarization of muscle fibers.

CLINICAL MANIFESTATIONS

Many of the effects of thallium poisoning are somewhat nonspecific and occur over a variable time course. When combined, however, a clear toxic syndrome can be defined (Table 96–1). Alopecia and a painful ascending peripheral neuropathy are the most characteristic findings. Unlike most other metal salt poisonings, gastrointestinal symptoms are usually modest or may even be absent in thallium poisoning. The most common symptom is abdominal pain,

TABLE 96–1. Clinical Manifestations of Acute Thallium Poisoning

	Onset of Effects			
Organ System	Immediate (<6 h)	Intermediate (Rarely in the first few days; within 2 wk)	Late (>2 wk)	Residual Effects
Gastrointestinal				
Nausea	†			
Vomiting	†			
Diarrhea	†			
Constipation	†	†		
Cardiovascular				
Nonspecific ECG changes	†	†		
Hypertension		†		
Tachycardia		†		
Respiratory				
Pleuritic chest pain	†	†		
Respiratory depression		†	†	
Renal				
Albuminuria		†		
Renal insufficiency		†		‡
Dermatologic				
Dry skin		†		
Alopecia		†		‡
Mees lines			†	‡
Neurologic				
Painful ascending sensory neuropathy		†	†	‡
Motor neuropathy		†	†	‡
Cranial nerve abnormalities		†		
Altered mental status		†		‡
Seizures		†	†	
Optic neuritis				‡
Memory and cognitive deficits				‡

† = Typical onset of symptoms.
The time course outlined above may be accelerated with extremely large doses.
When "†" appears in two adjacent columns, the time course is highly variable and may be dose dependent.
With small ingestions, many of the effects listed above may not be evident.
‡ = Effects that may persist long after exposure, and possibly permanently.

which is sometimes accompanied by vomiting and either diarrhea or constipation. Constipation may be a result of decreased intestinal motility and peristalsis, a result of direct involvement of the vagus nerve. Tachycardia and hypertension frequently occur and usually develop during the first or second week following an acute ingestion. A poor prognosis may be associated with

a persistent and pronounced tachycardia. Neurologic effects usually appear 2–5 days postexposure. Patients may present with severely painful, rapidly progressive ascending peripheral neuropathies. Pain and paresthesias are present in lower extremities (especially the soles of the feet), and although numbness is present in fingers and toes, there is also decreased sensation to pinprick, touch, temperature, vibration, and proprioception. Motor weakness is always distal in distribution, with the lower limbs more affected than the upper limbs.

Symptoms of confusion, delirium, psychosis, hallucinations, seizures, headache, insomnia, anxiety, tremor, ataxia, and choreoathetosis are common. Onset is variable and most likely dependent on dose. Ataxia can develop within 48 hours after ingestion. Insomnia occurs in almost every patient and may progress to total reversal of sleep rhythm. Coma may occur, especially with larger exposures. All cranial nerves—with the possible exception of I, V, and VIII—can be affected. Cranial nerve III involvement, as evidenced by ptosis, is common, and may be present asymmetrically. Nystagmus is another common finding.

Thallium is toxic to both the retinal fibers and the neural retina. Approximately 25% of patients may develop severe lesions of the optic nerve. Optic neuropathies can lead to optic atrophy and a permanent decrease in visual acuity. Renal function may remain normal in mild cases of thallium poisoning, even though the kidney bioaccumulates thallium to a greater extent than any other organ. Changes in renal function include oliguria, diminished creatinine clearance, elevated blood urea nitrogen, and albuminuria. Alopecia typically occurs as the presenting symptom in patients with chronic exposures. Facial and axillary hair, especially the inner one-third of the eyebrows, may be spared, but in some cases full beards, as well as all scalp hair, are lost. Dermatologic effects include acne, palmar erythema, and dry scaly skin that results from damage of the sebaceous glands. Mees lines appear within 2–4 weeks after exposure.

ASSESSMENT

Differential Diagnosis

The differential diagnosis of the neuropathy includes disorders such as poisoning by arsenic, colchicine, and vinca alkaloids; botulism; thiamine deficiency; HIV; and Guillain-Barré syndrome. Both the sensory neuropathy and the preservation of reflexes help differentiate thallium-induced neuropathy from Guillain-Barré syndrome and most other causes of acute neuropathy. When gastrointestinal symptoms are present along with neuropathy and other end-organ effects, poisoning with metal salts such as arsenic and mercury should be considered. The differential diagnosis of abrupt and complete alopecia is more restricted including radiation, arsenic, selenium, colchicine, and vinca alkaloid poisoning. When Mees lines are present, they indicate past exposure to metals, mitotic inhibitors, or antimetabolites, and as such are nonspecific for thallium.

Diagnostic Testing

Radiographs of tampered food products and the abdomen can document the presence of thallium. Although abdominal radiography may be useful shortly after a suspected exposure, the sensitivity and specificity of this test is unknown. Similarly, the yield from other routine studies such as the complete

blood count, electrolytes, urinalysis, and ECG are limited in that they are often normal, or demonstrate nonspecific findings at best. Microscopic inspection of the hair reveals a diagnostic pattern of black pigmentation of the hair roots of the scalp in approximately 95% of poisoned patients.

The definitive clinical diagnosis of thallium poisoning can only be established by demonstrating elevated thallium concentrations. Thallium can be recovered in the hair, nails, feces, saliva, blood, and urine. The standard toxicologic method is to obtain a 24-hour urine sample for thallium to be assayed by atomic absorption spectroscopy. Normal urine concentrations are below 5 μg/L.

MANAGEMENT

The treatment goals for a patient with thallium poisoning are identical to those of all poisoned patients: initial stabilization, prevention of absorption, and enhanced elimination.

Decontamination

Patients who present for healthcare shortly after ingestion should be considered candidates for orogastric lavage followed by activated charcoal. If the patient presents more than a few hours after ingestion or has had considerable spontaneous emesis, activated charcoal should be given. In patients with severe thallium toxicity, constipation is common, such that the addition of mannitol or another cathartic to the first dose of activated charcoal seems logical. Although no studies address the usefulness of whole-bowel irrigation with polyethylene glycol electrolyte lavage solution, this technique may prove useful, especially when radiopaque material is demonstrated in the gastrointestinal tract by an abdominal radiograph.

Potassium

Although once popular, forced potassium diuresis is associated with either the development or exacerbation of neurologic symptoms in humans and the exacerbation of lethality in animal models and thus should be avoided.

Chelation

Thallium toxicity does not respond to traditional chelation therapy with edetate calcium disodium ($CaNa_2EDTA$), dimercaprol (BAL), or D-penicillamine. Similarly, sulfur-containing compounds such as *N*-acetylcysteine (NAC) have no demonstrable benefit. Dithiocarb (sodium diethyldithiocarbamate) increases the urinary excretion of thallium, but also redistributes thallium into the central nervous system, potentially exacerbating neurologic symptoms.

Prussian blue is a crystal lattice of potassium ferric hexacyanoferrate ($KFe[Fe(CN)_6]$) and can be used as a chelator for thallium toxicity. It enhances survival in animals and increases elimination in humans. The dose of Prussian blue is 250 mg/kg/d orally via a nasogastric tube in 2–4 divided doses per day. If patients are constipated, the Prussian blue should be dissolved in 50 mL of 15% mannitol (see Antidotes in Brief: Prussian Blue).

Extracorporeal Drug Removal

Extracorporeal drug removal may have limited efficacy in patients with thallium toxicity, especially if begun shortly after the initial exposure while se-

rum concentrations remain high prior to effective tissue distribution. Data from a recent hemodialysis experience suggests that by using high blood flow rates (300 mL/min) clearances as high as 90–150 mL/min can obtained. Although clearances seem encouraging, this must be correlated with thallium's large volume of distribution. With lower blood flow rates, charcoal hemoperfusion may be 2–3 times more efficient than hemodialysis, providing clearance rates as high as 139 mL/min. Furthermore, combined hemoperfusion and hemodialysis was used in several cases and was reported to remove as much as 93 mg of thallium in 3 hours of therapy. Although extracorporeal therapy alone is probably insufficient for patients with significant poisoning and unnecessary in those with small exposures, it may be useful when used in combination with other therapies, especially in patients with renal insufficiency and in those with early massive and presumed lethal exposures. As is the case with other toxins, the use of peritoneal dialysis is probably ineffective in removing thallium.

Prussian Blue

The crystal lattice of Prussian blue takes up cations from the environment. Because its affinity increases as the ionic radius of the monovalent cation increases, Prussian blue preferentially binds cesium (ionic radius 0.169 nm) and thallium (ionic radius 0.147 nm) over potassium (ionic radius 0.133 nm). Thus, oral Prussian blue binds unabsorbed thallium or cesium in the gastrointestinal tract preventing absorption, and reversing the concentration gradient, thereby enhancing elimination through gut dialysis. In addition, Prussian blue interferes with enterohepatic circulation, causing a further reduction in tissue stores.

PHARMACOLOGY

Prussian blue is not absorbed from the gastrointestinal tract and is eliminated in the feces at a rate determined by gastrointestinal transit time. No significant food or drug interactions are known to exist. Animal studies show no adverse effects of therapeutic doses and oral lethal doses are unknown. The only significant adverse effects reported in humans from therapeutic doses are constipation and hypokalemia, and the constipation may be related more to the xenobiotic than the Prussian blue.

INDICATIONS

- Thallium poisoning
- Radioactive thallium poisoning
- Cesium poisoning
- Radioactive cesium poisoning

DOSAGE AND ADMINISTRATION

Thallium Poisoning

The dosage of Prussian blue has never been investigated systematically in either humans or animals. In most case reports and series, a total dose of 150–250 mg/kg/d is administered orally or via a nasogastric tube in 2–4 divided doses. Because constipation or obstipation is often present or expected in thallium poisoning, Prussian blue is generally dissolved in 50 mL of 15% mannitol. The manufacturer recommends that adults and adolescents with thallium poisoning receive a total dose of 9 g divided daily (3 g every 8 hours) and that children receive a total dose 3 g divided daily (1 g every 8 hours). Although the manufacturer does not suggest the use or benefit of a cathartic, the use of a high-fiber diet is advocated when constipation is present. Because Prussian blue is well tolerated, we continue to favor the 150–250 mg/kg/d dosing, as this provides more antidote.

The end point of therapy is similarly poorly defined. By convention, Prussian blue is usually continued until urinary thallium concentrations fall below 0.5 mg/d. This end point may not be a meaningful measurement of thallium burden, as fecal elimination may continue, even when urinary elimination has diminished.

Cesium Poisoning

There are no controlled trials of Prussian blue in radiocesium poisoning. Experience is derived exclusively from treating disaster victims. The manufacturer recommends that adults receive a total daily dose of 9 g divided into 3 g, 3 times per day. Children should receive a total daily dose of 3 g divided into 1 g, 3 times per day. Although these are the same doses used for thallium poisoning, therapy for cesium poisoning should be continued for at least 30 days. Quantitative and radiologic evaluations of cesium elimination should be performed to determine the end point of therapy.

PREGNANCY CATEGORY

Prussian blue is listed as pregnancy category C. Because of the severe consequences of poisoning and the lack of systemic absorption of Prussian blue, a risk-to-benefit analysis favors the use of the antidote in all poisoned pregnant patients.

AVAILABILITY

Insoluble Prussian blue (Radiogardase) is available as a 0.5-g blue powder in gelatin capsules for oral administration. It is manufactured by Haupt Pharma Berlin GmbH for distribution by Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG, Berlin.

97 Zinc

HISTORY AND EPIDEMIOLOGY

The Babylonians used zinc alloys more than 5000 years ago. Zinc oxide and zinc sulfate were used in Western Europe during the late 1700s and early 1800s for gleet (urethral discharge), vaginal exudates, and convulsions. In the late 1800s, brass workers who inhaled zinc oxide fumes were noted to develop "zinc fever," "brass founders' ague," or "smelter shakes," all of which are now identified as metal fume fever (Chap. 119).

Zinc salts enhance the solubility of pharmaceuticals such as insulin (eg, rapid insulin zinc, extended insulin zinc, and protamine zinc insulin). They are used in baby powder (zinc oxide), in sun blocks, and in topical burn preparations (zinc oxide). Zinc gluconate-containing lozenges are sold as dietary supplements to shorten the duration of the common cold. The FDA approved zinc acetate in 1997 for maintenance therapy of Wilson disease, a disorder of copper metabolism (Chap. 90).

Zinc is used in industry to enhance the durability of iron and steel alloys (galvanization) and is commonly used in construction. Inhalational zinc oxide exposures occur commonly in those who weld galvanized steel.

CHEMISTRY

Zinc is a divalent cation that is among the most common elements comprising the earth's crust. It has two common oxidation states: Zn^0 (elemental or metallic) and Zn^{2+}. The pure element exists as a blue to white shiny metal, but it also combines with other elements to form many familiar compounds: zinc chloride ($ZnCl_2$), zinc oxide (ZnO), zinc sulfate ($ZnSO_4$), and zinc sulfide (ZnS). Once the metal is exposed to moisture, it gets coated with zinc oxide or carbonate ($ZnCO_3$). Like other transition metals zinc is involved in reactions that generate reactive oxygen species with resultant tissue toxicity.

PHYSIOLOGY

Zinc is an essential nutrient and acts as a cofactor for more than 200 metalloenzymes (including acid phosphatase, alkaline phosphatase, alcohol dehydrogenase, carbonic anhydrase, superoxide dismutase, and both DNA and RNA polymerase), contributes to gene expression, has a role in membrane stabilization, vitamin A metabolism, and the development and maintenance of the nervous system. Zinc and copper concentrations generally have an inverse relationship in the plasma (Chap. 90). Zinc is also important in maintaining olfactory and gustatory function and normal fetal growth.

Zinc deficiency, or hypozincemia, is a well-described clinical entity. Physical findings that suggest the diagnosis include the triad of dermatitis (acral and perioral), diarrhea, and alopecia.

PHARMACOKINETICS AND TOXICOKINETICS

The average daily intake of zinc in the United States is 5.2–16.2 mg; foods that contain zinc include leafy vegetables (2 ppm) as well as meats, fish, and

poultry (29 ppm). The recommended daily allowance is 11 mg/d for men and 8 mg/d for women. Pregnant and nursing women require 12 mg/d.

The main site of oral zinc absorption is the jejunum, although it occurs throughout the intestine by either a metallothionein binding or zinc-protein complex in the luminal cells. Metallothioneins are specific metal-binding proteins that have diverse functions but are involved in essential metal homeostasis. Albumin binds about two-thirds of zinc in the plasma and the remainder is bound to α_2-globulins. The primary route of zinc excretion is fecal.

CLINICAL MANIFESTATIONS

The hallmark of acute zinc toxicity is gastrointestinal (GI) distress, including nausea, vomiting, abdominal pain and gastrointestinal bleeding. Zinc chloride, in concentrations greater than 20%, is particularly corrosive when ingested. Partial- and full-thickness burns to the oral mucosa, pharynx, esophagus, and stomach, as well as the laryngotracheal tree, may occur.

Acute inhalation of zinc chloride from smoke bombs produces lacrimation, rhinitis, dyspnea, stridor, and retrosternal chest pain. Upper respiratory tract inflammation, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) may occur, generally with no manifestaions of systemic absorption such as pathologic changes in the liver or kidneys. Inhalation of zinc oxide is associated with metal fume fever and not pneumonitis despite similar ambient zinc concentrations. This is likely related to water solubility of the zinc salt.

Rare reports of renal complications, hyperamylasemia, pancreatitis, and jaundice can be found. Certain zinc salts (such as zinc oxide), as found in baby powders, lotions, and calamine lotion, are nonirritating when applied to the skin and nontoxic when ingested.

Chronic zinc toxicity can produce a reversible sideroblastic anemia and a reversible myelodysplastic syndrome. Both anemia and granulocytopenia occur with the bone marrow showing vacuolated precursors and ringed sideroblasts. The mechanism appears to be a zinc-induced copper deficiency. To date, neither the International Agency for Research on Cancer (IARC) nor the Environmental Protection Agency (EPA) has classified zinc as carcinogenic.

Metal Fume Fever

Metal fume fever (MFF) typically occurs within 12 hours after an exposure to zinc fumes. Patients develop fever, chills, cough, chest pain, dyspnea, dry throat, and a metallic taste in the mouth. Although exposure to zinc oxide fume is the most common exposure associated with this syndrome, exposure to zinc compounds and other metal oxides may be implicated. The chest radiograph is commonly normal, although infiltrates may occur. Hypoxia and tachycardia are rare, but may also be noted. Overall, however, the syndrome is relatively benign with tolerance developing within days. An immune mechanism is suggested, and chronic exposure is needed for sensitization (Chap. 119).

DIAGNOSTIC TESTING

Because zinc is ubiquitous in the environment and laboratory, great care must be taken to avoid contamination of the samples. Because elevated zinc concentrations occur in the setting of copper deficiency, a serum copper concentration should always be obtained simultaneously. Whole blood zinc concentrations

exceed plasma concentrations by a ratio of approximately 6–7:1 because the metal accumulates in erythrocytes.

Urine zinc concentrations are not well defined. In a cohort of non-occupationally exposed Italians, the mean urine concentrations were 0.45 mg/L, with a range up to 0.85 mg/L. In the United States, normal urine values are generally accepted as less than 0.5 mg/d.

MANAGEMENT

Treatment for acute oral zinc toxicity is primarily supportive. Efforts should be focused on hydration as well as antiemetic therapy. Esophageal foreign bodies containing zinc may need to be removed if they do not pass spontaneously. Gastrointestinal decontamination after zinc salt ingestions may include whole-bowel irrigation (WBI).

The data regarding the efficacy of chelation therapy for zinc is limited in humans. Edetate calcium disodium ($CaNa_2EDTA$) was used successfully in several cases, as was the combination of $CaNa_2EDTA$ and dimercaprol (BAL). Both DTPA (diethylenetriaminepentaacetic acid) and EDTA enhance the urinary excretion of zinc in rodents. The urinary excretion of zinc increased 1.6–44-fold following a 3-mg/kg intravenous dose of DMPS (sodium 2,3-dimercapto-1-propane-sulfonate). Finally, an iron-chelating agent, deferiprone, was incidentally noted to cause decreased serum zinc concentrations in a transfusion overload study. Currently, either $CaNa_2EDTA$ alone or in combination with BAL seem the most reasonable choices (see Antidotes in Brief: Dimercaprol and Antidotes in Brief: Edetate Calcium Disodium).

Supportive care for patients with inhalational zinc exposures includes oxygen therapy and bronchodilators as clinically indicated. Ventilatory support may be required in severe cases. As metal fume fever is typically self-limited, nonsteroidal antiinflammatory drugs should be sufficient to relieve the transient discomfort.

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98 Antiseptics, Disinfectants, and Sterilants

An antiseptic is a chemical that is applied to living tissue to kill or inhibit microorganisms. Iodophors, chlorhexidine, and the alcohols (ethanol and isopropanol) are commonly used antiseptics. A disinfectant is a chemical or physical agent that is applied to inanimate objects to kill microorganisms. Bleach (sodium hypochlorite), phenolic compounds, and formaldehyde are examples of currently used disinfectants. Neither antiseptics nor disinfectants have complete sporicidal activity. A sterilant is a chemical or physical agent that is applied to inanimate objects to kill all microorganisms and also spores. Ethylene oxide and glutaraldehyde are examples of sterilants. Not surprisingly, many of the chemicals used to kill microorganisms also demonstrate considerable human toxicity. Table 98–1 summarizes the salient features of toxicity from this group of agents.

CHLORHEXIDINE

Few cases of deliberate oral ingestion of chlorhexidine are reported. Symptoms are usually mild and gastrointestinal irritation is the most likely effect after oral ingestion. Rare cases of hepatotoxicity and acute respiratory distress follow intentional ingestion and aspiration. Intravenous administration is associated with hemolysis and acute respiratory distress syndrome. Inhalation of vaporized chlorhexidine can cause methemoglobinemia.

HYDROGEN PEROXIDE

Hydrogen peroxide is an oxidizing agent that is generally available in two strengths: dilute hydrogen peroxide, with a concentration of 3–9% by weight (usually 3%), sold for home use; and concentrated hydrogen peroxide, with a concentration greater than 10%, used primarily for industrial purposes. Hydrogen peroxide has two main mechanisms of toxicity: local tissue injury and gas formation. Dilute hydrogen peroxide is an irritant and concentrated hydrogen peroxide is a caustic. Gas formation results when hydrogen peroxide interacts with tissue catalase, liberating molecular oxygen and water. One milliliter of 3% hydrogen peroxide liberates 10 mL of oxygen at standard temperature and pressure; 1 mL of the more concentrated 35% hydrogen peroxide liberates more than 100 mL of oxygen. Gas formation can result in life-threatening embolization.

Symptoms consistent with sudden oxygen embolization include rapid deterioration in mental status, cyanosis, respiratory failure, seizures, and myocardial ischemia. Clinical sequelae from the ingestion of dilute hydrogen peroxide are usually much more benign, with nausea and vomiting the most commonly reported symptoms.

TABLE 98–1. Antiseptics, Disinfectants, Sterilants, and Related Compounds

Chemical	Commercial Product	Use	Toxic Effects	Therapeutics and Evaluation
Acids				
Boric acid	Borax Sodium perborate Dobell's solution	Antiseptic Mouthwash Eyewash Roach killer	Blue-green emesis and diarrhea Boiled lobster appearance CNS depression; renal failure	GI decontamination Hemodialysis (rare)
Alcohols				
(Chaps. 75 and 103)				
Ethanol	Rubbing alcohol (70% ethanol)	Antiseptic Disinfectant	CNS depression Respiratory depression Dermal irritant	Supportive
Isopropanol	Rubbing alcohol (70% isopropanol)	Antiseptic Disinfectant	CNS depression Respiratory depression Ketonemia, ketonuria GI irritation/bleeding Hemorrhagic tracheobronchitis	Hemodialysis (rare)
Aldehydes				
Formaldehyde	Formalin 37% formaldehyde 12–15% methanol	Disinfectant Fixative Urea insulation	Caustic CNS depression Carcinogen	Gastric lavage Hemodialysis Sodium bicarbonate Endoscopy Folinic acid
Glutaraldehyde	Cidex (2% glutaraldehyde)	Sterilant	Mucosal and dermal irritant	Supportive
Chlorhexidine	Hibiclens	Antiseptic	GI irritation	Supportive
Chlorinated compounds				
Chlorates	Sodium chlorate Potassium chlorate	Antiseptic Matches Herbicide	Hemolytic anemia Methemoglobinemia Renal failure	Exchange transfusion Hemodialysis
Chlorine		Disinfectant	Irritant	Supportive

Chlorophors (sodium hypochlorite)	Hypochlorite bleach (5% NaOCl) Dakin solution(1 part 5% NaOCl, 10 parts H_2O)	Disinfectant Decontaminating solution	Mild GI irritation	Endoscopy (rare)
Ethylene oxide		Sterilant	Irritant; CNS depression Peripheral neuropathy Carcinogen?	Supportive
Mercurials (Chaps. 53 and 92)	Merbromin 2% (mercurochrome)	Antiseptic (obsolete)	CNS	Gastric lavage, AC, BAL, succimer
Iodinated compounds				
Iodine	Tincture of iodine 2% free iodine 2% sodium iodide 50% ethanol Lugol solution (5% I_2)	Antiseptic	Caustic	Milk, starch, sodium thiosulfate Endoscopy
Iodophors	Povidone-iodine (Betadine) (0.01% I_2)	Antiseptic	Limited	Same as iodine if symptomatic
Oxidants				
Hydrogen peroxide	H_2O_2 3%—household H_2O_2 30%—industrial	Disinfectant	Oxygen emboli GI caustic	Lavage Radiographic evaluation Endoscopy
Potassium permanganate	Crystals, solution	Antiseptic	Oxidizing agent, caustic, manganese elevation	Decontamination Endoscopy as needed
Phenols				
Nonsubstituted	Phenol (carbolic acid)	Disinfectant	Caustic Dermal burns Cutaneous absorption CNS effects	Decontamination: polyethylene glycol or water Endoscopy as needed
Substituted	Hexachlorophene	Disinfectant	Leucoencephalopathy	Supportive
Quaternary ammonium compounds				
Benzalkonium chloride	Zephiran	Disinfectant	GI caustic at high concentrations	Endoscopy if significant GI symptoms

Management

The treatment of patients with ingestions of concentrated solutions should include consideration of nasogastric aspiration of hydrogen peroxide if the patient presents immediately after ingestion and emesis has not occurred. Patients with abdominal distension from gas formation should also be treated with nasogastric suctioning. Those with clinical or radiographic evidence of gas in the heart should be placed in the Trendelenburg position to prevent gas from blocking the right ventricular outflow tract and referred for hyperbaric therapy.

IODINE AND IODOPHORS

Iodine usually refers to molecular iodine, also known as I_2, free iodine, or elemental iodine. Iodine is cytotoxic and an oxidant. Iodophors are substances in which molecular iodine is compounded to a high-molecular-weight carrier or to a solubilizing agent such as povidone. Iodophors limit the release of molecular iodine and are generally less toxic. Significant systemic absorption of iodine may result from topical iodine or iodophor preparations; however most reported toxicity follows ingestion.

Ingestion of iodine may cause abdominal pain, vomiting, diarrhea, GI bleeding, delirium, hypovolemia, anuria, and circulatory collapse. Severe caustic injury of the GI tract may occur. Reports of adverse consequences from iodophor ingestions are rare because of the reduced amount of available iodine. Hypernatremia, hyperchloremia, metabolic acidosis, and renal failure may occur. Contact dermatitis can result from repetitive applications of iodophors.

Careful nasogastric aspiration and lavage may be performed to limit the caustic effect of the iodine if signs of perforation are absent and spontaneous emesis has not occurred. Irrigation with a starch solution will convert iodine to the much less toxic iodide, and, in the process, turn the gastric effluent dark blue-purple. If starch is not available, milk may be a useful alternative. Activated charcoal adsorbs iodine and may be useful.

POTASSIUM PERMANGANATE

Potassium permanganate ($KMnO_4$) is a strong oxidizer that is sold either as a solid or a 0.01% solution. Historically, it was used as an abortifacient, urethral irrigant, lavage fluid for alkaloid poisoning, and snakebite remedy. Currently, potassium permanganate is most often used in baths and wet bandages as a dermal antiseptic, particularly for patients with eczema.

Potassium permanganate poisoning may result in local and systemic toxicity. Upon contact with mucous membranes, $KMnO_4$ reacts with water to form manganese dioxide, potassium hydroxide, and molecular oxygen. Local tissue injury is the result of contact with the nascent oxygen, as well as the caustic effect of potassium hydroxide. A brown-black staining of the tissues occurs from the manganese dioxide. Systemic toxicity may occur from free radicals generated by absorbed permanganate ions.

Following ingestion, initial symptoms include nausea and vomiting. Laryngeal edema and ulceration of the mouth, esophagus, and, to a lesser extent, the stomach may result from the caustic effects. Airway obstruction and fatal gastrointestinal perforation and hemorrhage may occur. Although $KMnO_4$ is not well absorbed from the GI tract, systemic absorption may occur, resulting in life-threatening toxicity. Systemic effects include hepatotoxicity, renal damage, methemoglobinemia, hemolysis, hemorrhagic pancreatitis, acute respira-

tory distress syndrome, disseminated intravascular coagulation, and cardiovascular collapse.

Because the effects of $KMnO_4$ ingestion are caused by the liberation of strong alkalis, the initial treatment of such a patient should include assessment for evidence of airway compromise. Further treatment is similar to that for other alkali injuries (Chap. 100).

CHLORINE AND CHLOROPHORS

Chlorine, one of the first antiseptics, is still used in the treatment of the community water supply and swimming pools. Chlorine is a potent pulmonary irritant that can cause severe bronchospasm and acute lung injury. Chapter 119 further discusses chlorine. Sodium hypochlorite, found in bleach and Dakin solution, remains a commonly used disinfectant. Toxicity from hypochlorite is mainly a result of its irritant effects. The ingestion of large amounts of household liquid bleach (5% sodium hypochlorite) on rare occasions can result in esophageal burns with subsequent stricture formation. The ingestion of a more concentrated "industrial strength" bleach preparation (eg, 35% sodium hypochlorite) increases the likelihood of local tissue injury and should be managed accordingly (Chap. 100).

MERCURIALS

Both inorganic mercurials, such as mercuric bichloride, and organic mercurials, such as merbromin (Mercurochrome) or thimerosal (Merthiolate), were used previously as topical antiseptics. Thimerosal contains 49% mercury. The relatively weak bacteriostatic properties, of mercurials as well as the many problems associated with mercury toxicity, significantly limit their usefulness (Chap. 53 and 92).

FORMALDEHYDE

Formaldehyde is a water-soluble, highly reactive gas at room temperature. Formalin consists of an aqueous solution of formaldehyde, usually containing approximately 37% formaldehyde and 12–15% methanol. Lethality in adults begins to occur following ingestion of 30–60 mL of formalin.

Formaldehyde is a potent caustic that may produce coagulation necrosis, protein precipitation, and tissue fixation. Ingestions of formalin may result in significant gastric injury, including hemorrhage, diffuse necrosis, perforation, and stricture. The most striking and rapid systemic manifestation of formaldehyde poisoning is metabolic acidosis, resulting both from tissue injury and from the conversion of formaldehyde to formic acid. The patient may present with profound acidemia, accompanied by a large anion gap metabolic acidosis (Chap. 103).

The immediate management of a patient who has ingested formaldehyde includes dilution with water. Careful gastric aspiration with a small bore nasogastric tube may limit systemic absorption and should be considered if spontaneous emesis has not occurred. Significant acidemia should be treated with fomepizole sodium bicarbonate and folinic acid (Chap. 103, Antidotes in Brief: Fomepizole, and Antidotes in Brief: Ethanol).

PHENOL

Phenol, also known as carbolic acid, is one of the oldest antiseptics. Phenol is also a component (0.1–4.5%) of various lotions, ointments, gels, gargles, loz-

enges, and throat sprays (Chap. 53). Although many cases of phenol poisoning were reported in the past, acute oral overdoses of phenol-containing solutions are relatively rare today. Phenol is a caustic that causes cell wall disruption, protein denaturation, and coagulation necrosis. It also acts a central nervous system stimulant. Severe dermal burns from phenol have resulted in systemic toxicity and even death within minutes to hours. Parenteral administration of phenol can also be lethal at a dose of as little as 1 g.

CNS effects include central stimulation, seizures, lethargy, and coma. Cardiac symptoms from phenol include tachycardia, bradycardia, and hypotension. Other systemic symptoms that may develop include pulmonary disturbances, hypothermia, metabolic acidosis, methemoglobinemia, and rabbit syndrome. Local toxicity to the GI tract from the ingestion of phenol may result in nausea, vomiting, bloody diarrhea, and severe abdominal pain. Dermal exposures to phenol usually result in a light brown staining of the skin.

A variety of treatments have been suggested for dermal and gastric decontamination of phenol. Low-molecular-weight polyethylene glycol solution (PEG 300 or 400) is the most effective decontaminating agent. Water is currently recommended for dermal irrigation and careful gastric decontamination. Water is a reasonable choice if PEG is unavailable. Supportive care is the mainstay of therapy for systemic toxicity.

SUBSTITUTED PHENOLS AND OTHER RELATED COMPOUNDS

Hexachlorophene is one of the best known substituted phenols. It was formerly used extensively as a disinfectant in hospitals until multiple cases of vacuolar encephalopathy and cerebral edema developed in children washed with this solution. Dermal contact with Dettol may result in full-thickness chemical burns. Cresol, a mixture of three isomers of methylphenol, has better germicidal activity than phenol and is a commonly used disinfectant. Exposure to concentrated cresol may result in significant local tissue injury, hemolysis, renal injury, hepatic injury, and CNS and respiratory depression. Treatment is mainly supportive.

QUATERNARY AMMONIUM COMPOUNDS

Quaternary ammonium compounds are cationic surfactants (surface-active agents) that are synthetic derivatives of ammonium chloride.

Quaternary ammonium compounds are generally of low toxicity with irritation and burns occurring infrequently. Rare reports of paralysis result from cholinesterase inhibition at the neuromuscular junction. Treatment is similar to that of other caustic ingestions.

ETHYLENE OXIDE

Ethylene oxide is a gas that is commonly used to sterilize heat-sensitive material in healthcare facilities. Ethylene oxide has a cyclic ester structure that acts as an alkylating agent, reacting with most cellular components, including DNA and RNA. Medical attention regarding ethylene oxide toxicity has centered on its mutagenic and possible carcinogenic effects. Approximately 270,000 workers (including 96,000 hospital workers) in the United States are at risk for occupational exposure to ethylene oxide. Retrospective studies suggest a possible excess incidence of leukemia and gastric cancer in ethylene oxide-exposed workers. It is also suggested that an increased incidence

of spontaneous abortions may be associated with occupational exposure to ethylene oxide.

The acute toxicity of ethylene oxide is mainly the result of its irritant effects. Conjunctival, upper respiratory tract, GI, and dermal irritation may occur. Dermal burns from acute exposure to ethylene oxide are reported. Chronic exposure to high concentrations of ethylene oxide may cause mild cognitive impairment and motor and sensory neuropathies. Treatment for patients with ethylene oxide exposure is supportive.

GLUTARALDEHYDE

Glutaraldehyde is a liquid solution used in the cold sterilization of nonautoclavable endoscopic, surgical, and dental equipment. It is also employed as a tissue fixative, embalming fluid, preservative, and tanning agent, in radiographic solutions, and in the treatment of warts. Approximately 35,000 workers are occupationally exposed to glutaraldehyde. Patients may be exposed when diagnostic instruments are inadequately rinsed following cold sterilization with glutaraldehyde.

Clinical signs and symptoms are thought to be comparable to those of formaldehyde exposure although human toxicity data is limited. Glutaraldehyde is also a mucosal irritant. Coryza, epistaxis, headache, asthma, chest tightness, palpitations, tachycardia, and nausea are all associated with glutaraldehyde vapor exposure. Contact dermatitis and ocular inflammation may also occur. Proctitis has been reported following the use of endoscopes contaminated with residual glutaraldehyde solution.

Treatment recommendations are similar to those for patients with formaldehyde exposure. Copious irrigation with water provides adequate dermal decontamination.

BORIC ACID

Boric acid is an odorless, transparent crystal although it is most commonly available as a finely ground white powder. Boric acid (H_3BO_3), prepared from borax (sodium borate; $Na_2\ B_4O_7 \bullet 10\ H_2O$), was first used as an antiseptic by Lister in the late 19th century. Boric acid is essentially obsolete in modern antiseptic therapy. However, it is commonly used in the treatment of cockroach infestation and as a soap, contact lens solution, toothpaste, and food preservative.

The exact mechanism of action of toxicity of boric acid remains unclear. Local effects are limited to tissue irritation. Classic boric acid poisoning usually involves multiple exposures over a period of days. The initial symptoms—nausea, vomiting, diarrhea, and occasionally crampy abdominal pain—may be confused with an acute gastroenteritis. At times, the emesis and diarrhea are greenish blue. Following the onset of GI symptoms, patients may develop a characteristic intense generalized erythroderma described as "boiled lobster" appearance. The rash may be especially noticeable on the palms, soles, and buttocks, and extensive desquamation occurs within 1–2 days. Seizures, delirium, and coma can occur. Renal injury is common, both as a result of the renal elimination of this compound and secondary to prerenal azotemia from GI losses.

Two large studies suggest that a single acute ingestion of boric acid is generally quite benign. Several reports suggest, however, that significant toxicity from massive acute ingestion of boric acid can occur. Long-term chronic exposure to boric acid results in alopecia in adults and seizures in children.

Treatment of boric acid toxicity is mainly supportive. Activated charcoal is not recommended because of its relatively poor adsorptive capacity for boric acid. In cases of massive oral overdose or renal failure, hemodialysis, or perhaps exchange transfusion in infants, may be helpful in shortening the half-life of boric acid. In patients with normal renal function, urine output should be maintained to assure maximal renal elimination.

CHLORATES

Sodium chlorate is a strong oxidizing agent. At one time, the chlorate salts, sodium chlorate and potassium chlorate, were used to treat inflammatory and ulcerative lesions of the oral cavity and could be found in various mouthwash, toothpaste, and gargle preparations. Although their use as local antiseptics is obsolete, chlorates are used as herbicides and in the manufacture of matches, explosives, and dyestuffs. More recent cases of chlorate poisoning resulted from the ingestion of the sodium chlorate-containing herbicides, or dispensing errors that confused sodium chlorate with sodium sulfate or sodium chloride.

The systemic effects of chlorates result from its ability to oxidize hemoglobin and increase red blood cell membrane rigidity. Consequently, significant methemoglobinemia and hemolytic anemia may result. Chlorates may also be directly toxic to the proximal renal tubule.

Clinical signs and symptoms of chlorate poisoning usually begin 1–4 hours after ingestion. The earliest symptoms are GI, including nausea, vomiting, diarrhea, and crampy abdominal pain. Subsequently, the patient may exhibit cyanosis from the methemoglobinemia and black-brown urine from the hemoglobinuria. Obtundation and anuria may ensue. Hyperkalemia may be particularly problematic if a patient ingests potassium chlorate.

Treatment of a patient with a significant chlorate ingestion should include orogastric lavage and the use of activated charcoal. Although methylene blue is used in the treatment of symptomatic methemoglobinemia, its efficacy in the treatment of chlorate-induced methemoglobinemia may be limited, secondary to direct inactivation of glucose-6-phosphate dehydrogenase. Exchange transfusion and hemodialysis may be required.

99 Camphor and Moth Repellents

Many different products have been used as moth repellents. In the United States, paradichlorobenzene has largely replaced both camphor and naphthalene as the most common component of mothballs and moth flakes because it is less toxic. However, both naphthalene and camphor are still available.

CAMPHOR

Camphor has been used as an aphrodisiac, contraceptive, abortifacient, suppressor of lactation, analeptic, cardiac stimulant, antiseptic, cold remedy, muscle liniment, and drug of abuse. Camphorated oil and camphorated spirits contain varying concentrations. Historically, most camphorated oil was 20% weight (of solute) per weight (of solvent) (w/w) camphor with cottonseed oil and most camphorated spirits contained 10% w/w camphor with isopropyl alcohol. Today, based on a 1983 FDA ruling, nonprescription camphor products may not contain greater than an 11% concentration of camphor. Camphorated oil is still used as an herbal remedy and muscle liniment, and products containing more than 11% camphor can be purchased legally outside of the United States.

Pharmacology and Pathophysiology

Camphor (2-bormanone, 2-camphonone) is a cyclic ketone of the terpene group. The pharmacologic activity of camphor is not well studied and its mechanism of action remains unclear.

Pharmacokinetics and Toxicokinetics

There are limited data on the pharmacokinetics and toxicokinetics of camphor. Camphor toxicity is reported following ingestion, dermal application, inhalation, intranasal instillation, intraperitoneal administration, and transplacental transfer. Ingestion of solid camphor also causes toxicity. Liquid camphor preparations are rapidly absorbed from the gastrointestinal tract. Camphor is highly lipid soluble and is predominantly metabolized in the liver where it undergoes hydroxylation followed by conjugation with glucuronic acid. Inactive metabolites, including campherol, borneol, hydroxy-camphor, and camphoglycuronic acid, are excreted by the kidneys.

Although the toxic dose is not well delineated, as little as 1 teaspoon (1 g) of 20% camphorated oil has been reported to cause death in an infant.

Clinical Manifestations

Exposure can often be detected by its characteristic aromatic odor. Ingestion typically produces oropharyngeal irritation, nausea, vomiting, and abdominal pain. Generalized tonic-clonic seizures may be the first sign of camphor toxicity, usually occurring within minutes to 1–2 hours postingestion. Most seizures are brief and self-limited, although some patients may have a more protracted course.

Acute ingestions of camphor can also cause transient elevations of the liver enzymes. Chronic administration can cause altered mental status and elevated hepatic aminotransferase concentrations suggestive of Reye syndrome.

Camphor crosses the placenta. Both fetal demise and delivery of healthy neonates are reported in mothers experiencing camphor toxicity within 24 hours of term delivery.

Inhalation and dermal exposure usually produce only mucous membrane irritation and dermal irritation, respectively.

Diagnostic Testing

Camphor and hydroxylated metabolites can be identified in blood. Camphor and camphoglycuronic acid can be identified in urine. However, these camphor concentrations are not useful when managing most patients.

Management

Nasogastric suctioning and lavage seem preferable to orogastric lavage following a recent substantial ingestion of most liquid preparations of camphor. Emesis should not be induced as seizures can occur rapidly, increasing the risk for pulmonary aspiration. Administration of activated charcoal, 1 g/kg, is likely to be safe, although its efficacy is unstudied.

Patients with camphor-induced seizures should be treated with benzodiazepines and/or barbiturates. Repeat doses of benzodiazepines may be needed to control seizures. If benzodiazepines fail to control seizures, a barbiturate, such as phenobarbital, should be administered.

Data suggest that hemodialysis with a lipid dialysate and either hemoperfusion using an Amberlite resin or charcoal hemoperfusion can remove camphor. However, because most toxicity is short-lived, these techniques are unlikely to be useful.

NAPHTHALENE

Naphthalene is a bicyclic aromatic hydrocarbon that is pure white and has a noxious odor. Most unintentional exposures to naphthalene-containing mothballs occur in children and do not cause life-threatening toxicity.

Pharmacology, Pharmacokinetics, and Toxicokinetics

Naphthalene toxicity is reported following ingestion, dermal application, and inhalation. Although naphthalene's absorption is not well studied, highly lipid-soluble compounds may increase the absorption of naphthalene. Once absorbed, it is slowly metabolized in the liver to α- and β-naphthol and to α- and β-naphtholoquinone. These hepatic metabolites (predominantly α-naphthol) are potent oxidants that are responsible for the major toxic effects of naphthalene. While the reported toxic dose is highly variable, it is generally accepted that as little as one naphthalene mothball can produce toxicity in a susceptible child.

Pathophysiology

Oxidant stress can cause methemoglobinemia and/or hemolysis. When oxidant stress causes iron on hemoglobin to be converted from the ferrous state (Fe^{2+}) to the ferric state (Fe^{3+}) state, methemoglobin is formed. This simple change renders hemoglobin incapable of carrying oxygen. When oxidant stress causes hemoglobin denaturation, the heme groups and the globin chains dissociate and precipitate in the erythrocyte, forming Heinz bodies.

An erythrocyte with denatured hemoglobin is more susceptible to hemolysis and to removal by the reticuloendothelial system.

The most important protective mechanism against oxidants involves the generation of reduced nicotine adenine dinucleotide phosphate (NADPH), which is used to maintain a supply of reduced glutathione, the major intracellular reducing agent. The hexose monophosphate shunt is used to produce NADPH. NADPH is formed when glucose-6-phosphate dehydrogenase (G6PD) converts glucose-6-phosphate to 6-phosphogluconate. Patients with varying degrees of G6PD deficiency are more susceptible to both hemolysis and methemoglobinemia following oxidant stress, with hemolysis occurring more frequently in this subset of patients.

Clinical Manifestations

Acute and chronic exposures to naphthalene result in similar toxicity. Ingestion and inhalational exposures to naphthalene commonly cause headache, nausea, vomiting, diarrhea, abdominal pain, fever, and altered mental status. Hemolysis and or methemoglobinemia usually do not become clinically evident before 1–2 days postexposure. Anemia secondary to hemolysis often does not reach its nadir until 3–5 days postexposure.

Signs and symptoms of hemolysis and methemoglobinemia are nonspecific and include tachycardia, tachypnea, shortness of breath, generalized weakness, decreased exercise tolerance, and altered mental status. Methemoglobinemia may produce cyanosis, whereas hemolysis may produce pallor, jaundice, and dark urine.

Diagnostic Testing

Both naphthalene and its metabolites can be identified in blood and urine, but provide no valuable information for managing acute exposures. Blood should be sent for cooximetry if methemoglobinemia is suspected. Hemoglobin, bilirubin, lactate dehydrogenase, haptoglobin, and urinalysis, may help diagnosis hemolysis. Examination of a peripheral blood smear can reveal evidence of hemolysis before a patient develops clinical or laboratory evidence of anemia. Testing for G6PD activity is not recommended during an acute episode of hemolysis because young erythrocytes have higher G6PD activity than do older red blood cells and a false negative test may result.

Management

Most patients with an unintentional exposure to one or part of one naphthalene-containing mothball do not require evaluation. Patients who should be evaluated include those who recently ingested more than one naphthalene-containing mothball, anyone with signs or symptoms of hemolysis and/or methemoglobinemia, patients with known or suspected G6PD deficiency, all intentional ingestions, and patients with large inhalational exposures, especially those occurring in an occupational setting.

Most patients with unintentional exposures do not require gastrointestinal decontamination. Administration of activated charcoal, 1 g/kg, although not of proven efficacy, is also reasonable for patients with large ingestions.

Patients with laboratory evidence of hemolysis should be closely observed and only transfused for life-threatening anemia. Most patients typically re-

cover quickly as young erythrocytes are resistant to hemolysis. Patients with significant methemoglobinemia should receive intravenous methylene blue, 1–2 mg/kg (0.1–0.2 mL/kg of a 1% solution) (see Antidotes in Brief: Methylene Blue).

PARADICHLOROBENZENE

Paradichlorobenzene is the most common component of moth repellents and is also found in deodorizers and disinfectants.

Pharmacology, Pharmacokinetics, Toxicokinetics, and Pathophysiology

Paradichlorobenzene is pure white and has a noxious odor. The mechanism for the effects of paradichlorobenzene, its pharmacology, and its toxicokinetics have not been studied.

Clinical Manifestations

Inhalation of paradichlorobenzene may cause nausea and vomiting, headache, and mucous membrane irritation. Most patients who ingest paradichlorobenzene develop only self-limited gastrointestinal distress.

Case reports associate chronic exposure to paradichlorobenzene with weight loss, ataxia, pulmonary granulomatosis, dyspnea, hepatotoxicity, anemia, and fixed drug eruptions.

Diagnostic Testing

Both paradichlorobenzene and its metabolite, 2,5-dichlorophenol, can be identified in blood and urine following exposure, but have no role in acute poisoning. Quantifying the amount of paradichlorobenzene in the urine of workers may be useful for monitoring occupational exposures.

Management

Because most unintentional exposures to paradichlorobenzene do not cause significant toxicity, evaluation by health professionals is unnecessary. Likewise, routine gastrointestinal decontamination should be considered to be potentially more harmful than beneficial.

MOTHBALL RECOGNITION

It may be clinically useful to distinguish naphthalene, paradichlorobenzene, and camphor. The easiest way to differentiate camphor mothballs from either naphthalene or paradichlorobenzene mothballs is to place the mothball in water. Mothballs made of naphthalene or paradichlorobenzene sink, whereas mothballs made of camphor float. Naphthalene mothballs can then be differentiated from paradichlorobenzene mothballs by placing the mothball in water that is saturated with table salt (sodium chloride). Naphthalene and camphor mothballs float, whereas paradichlorobenzene mothballs sink.

100 Caustics

HISTORY AND EPIDEMIOLOGY

As early as 1927, regulatory legislation in the United States governing the packaging of lye and acid containing products mandated that warning labels be placed. In response to the recognition that caustic exposures were more frequent in children, in 1970 the Federal Hazardous Substances Act and Poison Prevention Packaging Act was passed, stating that all caustics with a concentration greater than 10% must be placed in child-resistant containers. By 1973, the household concentration for child-resistant packaging was lowered to 2%.

Typically, children are unintentionally exposed to household products. Adults may be intentionally or unintentionally exposed to household or industrial products. Although children comprise 39% of admissions for caustic ingestions, adults comprise 81% of patients requiring treatment.

PATHOPHYSIOLOGY

A caustic is a substance that causes both functional and histologic damage on contact with tissue surfaces. Caustics are typically classified as acids or alkalis. An acid is a proton donor and causes significant tissue injury when the pH is below 3. An alkali is a proton acceptor and causes significant tissue injury when the pH is above 11. Zinc chloride and phenol are capable of producing severe burns even though they have near physiologic pH. The extent of injury is determined by duration of contact; ability of the substance to penetrate tissues; volume, pH, and concentration of the caustic; and a variety of other factors. Neutralization of caustics takes place at the expense of the tissues, resulting in the release of thermal energy producing further burns.

Following exposure to alkalis, dissociated hydroxide (OH^-) ions penetrate tissue surfaces producing what is histologically described as liquefactive necrosis. This process includes protein dissolution, collagen destruction, fat saponification, cell membrane emulsification, transmural thrombosis, and cell death. Erythema and edema occur within seconds followed by an inflammatory reaction.

In contrast, following exposure to an acid, hydrogen (H^+) ions desiccate epithelial cells, producing an eschar, resulting in what is histologically referred to as coagulation necrosis. This process leads to edema, erythema, mucosal sloughing, ulceration, and necrosis of tissues. Dissociated anions of the acid (Cl^-, SO_4^{2-}, PO_4^{3-}) also act as reducing agents further injuring tissue.

Classification and Progression of Caustic Injury

Esophageal injuries are classified based on endoscopic visualization and employ a grading system similar to that used with of burns of the skin. Grade I burns are generally described as hyperemia or edema of the mucosa without evidence of ulcer formation. Grade II burns include submucosal lesions, ulcerations, and exudates. These lesions can be further divided into grade IIa, noncircumferential lesions, and grade IIb, near-circumferential injuries. Grade III burns are defined as deep ulcers and necrosis into the periesophageal tissues.

A consistent pattern of injury and repair follow caustic injury. As wound healing occurs, neovascularization and fibroblast proliferation take place, laying down new collagen and replacing the damaged tissue with granulation tissue. Burns of the esophagus may persist for up to 8 weeks as remodeling takes place and may be followed by esophageal shortening. If the initial injury penetrates deeply enough, there is progressive narrowing of the esophageal lumen. The dense scar formation results in a stricture, which can evolve over a period of weeks to months and lead to dysphagia and significant nutritional deficits. Grade I burns carry no risk of stricture formation. Grade II circumferential burns lead to stricture formation in approximately 75% of cases. Grade III burns invariably progress to stricture formation and are also at a high risk of perforation.

Clinical Presentation

The gastrointestinal tract, respiratory tract, eyes and skin of a patient can all be sites of caustic injury, which may produce severe pain on contact with any of these tissues. By far, the majority of long-term morbidity and mortality from caustic exposure results from ingestion.

In general, patients who have ingested alkalis or acids have similar initial presentations that consists of severe pain of the lips, mouth, throat, chest, or abdomen. Oropharyngeal edema and burns may lead to drooling and rapid airway compromise. Symptoms of esophageal involvement include dysphagia and odynophagia, whereas epigastric pain and hematemesis may be symptoms of gastric involvement.

Respiratory tract damage may occur through direct inhalation or aspiration of vomitus leading to the clinical manifestations of hoarseness, stridor, and respiratory distress. Injury may result in epiglottitis, laryngeal edema and ulceration, pneumonitis, and impaired gas exchange. Patients may also be tachypneic or hyperpneic as a compensatory response to the metabolic acidosis generated by elevated lactate from necrotic tissue or hemodynamic compromise.

Predictors of Injury

Large studies demonstrate that the presence of visible injury of the cheeks, lips, or oropharynx is not a prerequisite for gastrointestinal injury. In fact more than one third of children with no visible lesions are found to have esophageal lesions on endoscopy. The abdominal examination is likewise an unreliable indicator of the severity of injury. The absence of pain or findings on abdominal examination does not preclude life-threatening gastrointestinal damage, especially following acid ingestion. However, in children with unintentional ingestions of alkali the presence of two or more of the findings of vomiting, drooling, and stridor is highly predictive of a significant esophageal injury. Stridor is nearly 100% specific for significant esophageal injury. Also, the absence of these findings has a high negative predictive value.

Although endoscopy is usually performed in all patients with intentional ingestions, the above clinical findings support observation of children with unintentional caustic ingestions who remain completely asymptomatic and tolerate liquids.

Although the risk of carcinoma after caustic ingestions is inadequately studied, long-term survivors of moderate and severe injury of the esophagus have a risk of esophageal carcinoma that is 1000 times greater than that of the general population and carcinomas present with a latency of up to 40 years. Regular endoscopy is required to detect early lesions.

DIAGNOSTIC TESTING

Laboratory

All patients with presumed caustic exposure should have evaluation of blood pH, blood type and crossmatch, hemoglobin, coagulation parameters, electrolytes, and urinalysis. Elevated prothrombin (PT) and partial thromboplastin times, as well as an arterial pH lower than 7.22, are associated with severe caustic injury. Absorption of nonionized acid from the stomach mucosa may result in acidemia. Following ingestion of hydrochloric acid, hydrogen and chloride ions (both of which are accounted for in the measurement of the nonanion gap) dissociate in the serum resulting in a hyperchloremic anion gap metabolic acidosis. Other acids, such as sulfuric acid, result in an elevated anion gap metabolic acidosis because the anion, sulfate is not measured in the calculation of the anion gap. Although alkalis are not absorbed systemically, necrosis of tissue may result in a metabolic acidosis from an elevated lactate.

Radiology

Chest and abdominal radiographs are useful in the initial stages of management to detect gross signs of esophageal or gastric perforation. Signs of perforation include pneumomediastinum, pneumoperitoneum, and pleural effusion. CT is considerably more sensitive than radiography for detecting viscus perforation and should be obtained in patients with potentially serious caustic ingestions, especially when endoscopy is delayed or unavailable. Unfortunately, other than diagnosing perforation, neither contrast esophagram nor contrast CT scan are sufficiently sensitive or specific for diagnosing mucosal injury. The major role of radiographic imaging is to noninvasively follow the patient after initial evaluation and stabilization. For example, contrast radiography is routinely used in the weeks or months following a caustic ingestion to detect esophageal narrowing representing stricture formation.

Endoscopy

Endoscopy should be performed within 12 hours and generally no later than 24 hours after ingestion. Numerous case series demonstrate that the procedure is safe during this period. Early endoscopy serves multiple purposes in that it allows patients with minimal or no evidence of gastrointestinal injury to be discharged. It also offers a rapid means of obtaining diagnostic and prognostic information while shortening the period of time that patients forego enteral nutritional support, permitting more precise treatment regimens. The use of endoscopic assessment from the second or third day postingestion is discouraged and should be avoided from 5 days to 2 weeks as it is at this time that wound strength is least and the risk of perforation is greatest.

A prospective evaluation of the role of fiberoptic endoscopy in the management of caustic ingestions recommended the following guidelines: (a) direct visualization of the esophagus prior to advancing the instrument, (b) minimal insufflation of air, (c) passage into the stomach unless there is a severe (particularly circumferential) esophageal burn, and (d) avoidance of retroversion or retroflexion of the instrument within the esophagus. The absence of burns in the esophagus does not imply that severe necrosis and ulcerations do not exist in the stomach and duodenum. In the case of termination of endoscopy because of grade IIb or grade III esophageal burns, barium studies, CT, or

consideration of surgical exploration should be undertaken to visualize remaining structures.

MANAGEMENT

Acute Management

Initial stabilization should always begin with assessment and stabilization of the airway. Direct visual inspection of the vocal cords with a fiberoptic laryngoscope may reveal signs of impending airway compromise. Although unstudied, most clinicians agree that patients with signs of caustic-induced airway edema benefit from dexamethasone 10 mg IV in adults, and 0.6 mg/kg up to a total dose of 10 mg in children. Careful and constant attention to signs and symptoms of respiratory distress and airway edema, such as stridor and change in voice, is mandatory and should prompt intubation as airway edema may rapidly progress over minutes to hours. A delay in protection may make subsequent attempts at intubation or bag-valve mask ventilation difficult or impossible. Nonsurgical airway placement is recommended whenever possible, as both cricothyrotomy and tracheostomy will interfere with the surgical field if esophageal repair is required. Intubation is best performed by either direct laryngoscopy or fiberoptic endoscopy. Blind nasotracheal intubation is absolutely contraindicated. Paralytic agents should be avoided as airway edema and bleeding may distort the ability to successfully ventilate via bag-valve mask.

Following control of the airway, additional large-bore intravenous access should be secured and volume resuscitation initiated. "Third spacing" of intravascular fluid to the interstitial space may result in hypotension. Empiric rehydration with clinical assessment of central venous pressures and neck vein distension should be used to guide individual fluid requirements.

Decontamination, Dilution, and Neutralization

Decontamination should begin with careful, copious irrigation of the patient's skin and eyes, when indicated, to remove any residual caustic and to prevent contamination of other patients and staff. Beyond the first few moments following ingestion, dilutional therapy is of limited benefit. A child who refuses to swallow or take oral liquids should never be forced to do so. In general, dilutional therapy should be limited to patients who have no airway compromise, who are not complaining of significant pharyngeal, chest, or abdominal pain, who are not vomiting, and who are alert. Dilutional therapy should be avoided in patients with nausea, drooling, stridor or abdominal distension as it may induce vomiting.

Gastrointestinal decontamination is usually limited in the patient with a caustic ingestion. Induced emesis is contraindicated, and adsorption to activated charcoal is inconsequential. Gastric emptying via cautious placement of a narrow nasogastric tube with gentle suction may be attempted in patients with large intentional ingestions of acid who present within 30 minutes of ingestion and who have had no spontaneous emesis. This technique is contraindicated with alkaline ingestions.

Exceptions to the general rules of gastrointestinal decontamination of caustics exist in the management of zinc chloride ($ZnCl_2$) and mercuric chloride ($HgCl_2$). Both are corrosives with severe systemic toxicity causing life-threatening illness from cationic metal exposure. The local corrosive effects, although of great concern, are less consequential than the manifestations of systemic absorption. For this reason, aggressive decontamination with gentle

nasogastric tube aspiration and administration of activated charcoal should be accomplished.

Attempts at neutralization of caustics should be avoided. This technique has the potential to worsen tissue damage by forming gas and generating an exothermic reaction.

Surgical Management

Surgical management is indicated in the presence of either endoscopic or diagnostic imaging evidence of perforation, severe abdominal rigidity, persistent hypotension, or severe extensive burns. Multiple studies have attempted to codify the signs and symptoms necessary or sufficient to rapidly identify patients who would benefit from surgery, but who lack clear clinical indications. Several retrospective and prospective series of caustic ingestions found that patients with large ingestions (greater than 150 mL), shock, acidemia, or coagulation disorders had severe findings on surgical exploration. These studies also reinforce that the abdominal examination was frequently unreliable in predicting the need for surgery.

Surgical intervention may include laparotomy for tissue visualization, resection, and repair of perforations. Laparoscopy may also be used, although it may not allow inspection of the posterior aspect of the stomach.

Subacute Management

Grade I Esophageal Injuries

Patients with isolated grade I injuries of the esophagus do not develop strictures and are not at increased risk of carcinoma. Their diet can be resumed as tolerated. No further therapy is required. These patients can be discharged from the hospital as long as they are able to eat and drink and their psychiatric status is stable.

Grade IIa Esophageal Injuries

If endoscopy reveals grade IIa lesions of the esophagus and sparing of the stomach, a soft diet can be resumed as tolerated, or a nasogastric tube can be passed under direct visualization. If oral intake is contraindicated because of the risk of perforation, feeding via gastrostomy, jejunostomy, or total parenteral nutrition should be instituted as rapidly as possible.

Grades IIb and III Esophageal Injuries

Patients with grades IIb and III lesions must be followed for the complications of perforation, infection, and development of strictures. Additionally, patients with grade III burns are also at high risk for other complications, including fistula formation, infection, and perforation with associated mediastinitis and peritonitis.

A variety of strategies have been used in an attempt to prevent strictures and esophageal obstruction. Currently, most authors agree that there is no role for administration of steroids for any degree of gastrointestinal injury. Intraluminal stents and nasogastric tubes can successfully maintain the patency of the esophageal lumen. For nutritional support, the stents are usually attached to a feeding tube secured in the nasopharynx through which the patient can receive feedings without interfering with esophageal repair. Numerous other therapies have been tried with little success.

Chronic Treatment of Strictures

Commonly, the management of esophageal strictures includes early endoscopic dilation for which a variety of types of dilators are available. Multiple dilations are often necessary. In one study, patients with a maximal esophageal wall thickness of 9 mm or greater required more than seven sessions to achieve adequate dilation.

Management of Ophthalmic Exposures

Ophthalmic exposures frequently occur from splash injuries and, more recently, from the alkaline by-products of sodium azide released in automobile air bag deployment and rupture. The mainstay of therapy for these patients is immediate irrigation of the eye for a minimum of 15 minutes with 0.9% sodium chloride, lactated Ringer solution, or tap water, if it is the only agent immediately available. Several liters of irrigation fluid are recommended. Anterior chamber irrigation may be required and should be performed emergently by an ophthalmologist. A thorough eye examination should be completed and follow-up arranged (Chap. 20).

101 Hydrofluoric Acid and Fluorides

HISTORY AND EPIDEMIOLOGY

Hydrofluoric acid (HF) has been known for centuries for its ability to dissolve silica. HF currently has multiple uses, such as brick cleaning, etching microchips in the semiconductor industry, electroplating, leather tanning, rust removal, and the cleaning of porcelain.

Hydrofluoric acid is also the most common cause of fluoride poisoning, although other forms of fluoride, including sodium fluoride (NaF) and ammonium bifluoride (NH_4HF_2), may also produce significant toxicity. Exposures to the hand are by far the most common presentation. Exposures to HF are also often an occupational hazard.

CHEMISTRY

Hydrofluoric acid can cause life-threatening complications following seemingly trivial exposure. Anhydrous HF is highly concentrated (>70%) and used almost exclusively for industrial purposes. The aqueous form of HF which generally ranges in concentrations from 3–40% is commonly used in both industrial and household products. The pK_a of HF is 3.5 and as such, it is classified as a weak acid. Therefore, it is approximately 1000 times less dissociated than equimolar hydrochloric acid.

PATHOPHYSIOLOGY

Exposures to HF occur via dermal, ophthalmic, inhalational, and oral routes, with even one reported case of toxicity from an HF enema. A high permeability coefficient allows HF to penetrate deeply into tissues prior to dissociating into hydrogen ions and highly electronegative fluoride ions. These fluoride ions avidly bind to intracellular stores of calcium and magnesium, ultimately leading to cellular dysfunction and cell death. Additionally, fluoride interferes with many enzyme systems by binding with magnesium and manganese. The minimal lethal dose in humans is approximately 1 mg/kg of fluoride.

CLINICAL MANIFESTATIONS

Local Effects

Skin

The extent of tissue injury in dermal exposures is determined by the volume, concentration, and contact time with the tissues. Dermal exposures to HF typically involve low concentrations. The higher the concentration of HF, the more rapid the onset of excruciating pain at the site of contact. Concentrations of greater than 50% cause immediate pain with visible tissue damage. Because household rust-removal products have concentrations ranging between 6–12% there is often a delay of several hours following exposure before the onset of pain. The initial site of injury may appear benign, despite significant subjective complaints of pain. Over time, the tissue becomes hyperemic, with subsequent blanching and coagulative necrosis. If more than

2–3% of the body surface area is exposed to high concentration HF, life-threatening systemic toxicity should be expected.

Pulmonary

Patients with inhalational exposures can present with a variety of signs and symptoms depending upon the HF concentration and exposure time. Exposure to low-concentration HF produces minor upper respiratory tract irritation, whereas larger exposures produce throat burning, shortness of breath, and hypoxemia. Stridor, wheezing, rhonchi, and erythema and ulcers of the upper respiratory tract, are also described. Systemic toxicity may result from inhalation. Ophthalmic exposure should always be considered in patients with inhalational exposure.

Gastrointestinal

Intentional ingestion of concentrated HF (or other fluoride compounds such as NaF) causes significant gastritis while often sparing the remainder of the gastrointestinal tract. Patients promptly develop vomiting and abdominal pain. Systemic absorption is rapid and almost invariably fatal. Following HF ingestion patients may present with an altered mental status, airway compromise, and dysrhythmias.

Ophthalmic

Hydrofluoric acid causes more extensive injury to the eye than do most other acids. HF denudes the corneal and conjunctival epithelium and leads to stromal corneal edema, conjunctival ischemia, sloughing, and chemosis. Fluoride ions penetrate deeply to affect the anterior chamber structures.

Systemic Effects

Fatal exposures to HF are characterized by hypocalcemia, hypomagnesemia, and, in many cases, hyperkalemia. The hypocalcemia may disrupt the coagulation cascade resulting in coagulopathy. However, the terminal event is usually described as the sudden-onset of myocardial conduction failure and ventricular fibrillation. Although electrolyte abnormalities may produce these dysrhythmias, evidence suggests that HF also directly impairs myocardial function.

DIAGNOSTIC TESTING

Following significant exposure, ionized calcium should be serially monitored along with magnesium and potassium. Additional information may be obtained from a venous or arterial blood-gas analysis. As systemic toxicity progresses, there is potential for development of metabolic acidosis. Serum fluoride concentrations may be assessed, but the results will not be returned in a clinically relevant timeframe. Although a serum fluoride concentration of 0.3 mg/dL has been reported as fatal, one patient survived with a serum fluoride concentration of 1.4 mg/dL.

Electrocardiographic findings of both hypocalcemia (prolonged QTc) and hyperkalemia (peaked T waves), may be reliable indicators of cardial toxicity (Chap. 5).

MANAGEMENT

General

For all types of exposures, the mainstay of management is to prevent or limit systemic absorption, assess for systemic toxicity, and rapidly correct any

electrolyte imbalances. Rapid airway assessment and protection should occur early in patients with severe inhalational injury, respiratory distress, ingestion with vomiting, or burns significant enough to cause a change in mental status. Intravenous access should be obtained. An ECG should be examined for signs of hypocalcemia, hypomagnesemia, and hyperkalemia, and the patient should undergo continuous cardiac monitoring. Rapid determinations of serum electrolytes will help guide replacement therapy in conjunction with the ECG.

To prevent absorption from dermal exposures, irrigation should be performed with copious amounts of water.

Local Dermal Toxicity

Dermal burns are exceedingly painful and analgesics are indicated. Additionally, a topical calcium gel should be applied to the affected area. This gel is prepared by mixing 3.5 g of calcium gluconate powder in 5 ounces of sterile water-soluble lubricant, or 25 mL of 10% calcium gluconate in 75 mL of sterile water-soluble lubricant. If calcium gluconate is unavailable, calcium chloride or calcium carbonate can be used in a similar formulation. Topical calcium therapy scavenges fluoride ions, limiting both local and systemic effects. Other therapies to limit local effects include intradermal and intraarterial calcium administration.

If topical gel therapy fails to decrease pain within the first few minutes of application, intradermal administration of calcium gluconate should be considered. This treatment may have limited usefulness, however, in small spaces, such as fingertips. The preferable method is to approach the wound from a distal point of injury and inject intradermally no more than 0.5 mL/cm^2 of 5% calcium gluconate.

If the wound is large, in a section of the fingerpad, or in an area that is not amenable to intradermal injections, consideration should be given to the use of intraarterial calcium gluconate. This procedure delivers calcium directly to the affected tissue from a proximal artery. Placement should be ipsilateral and proximal to the affected area, usually in the radial or brachial artery. Confirmatory angiography should be considered if cannulation is difficult or a good pressure tracing is not obtained. The recommended protocol consists of 10 mL of 10% calcium gluconate added to either 40 mL of 5% dextrose in water (D_5W) or 0.9% NaCl solution to infuse over 4 hours. Repeated treatments may be required, based on the patient's pain response.

Other reported therapies for localized HF poisoning include an intravenous Bier-block technique that uses 25 mL of 2.5% calcium gluconate. In one case, the effects lasted 5 hours and there were no adverse events. Although the intravenous Bier-block technique is not widely reported, it may be particularly useful when intraarterial infusion is problematic. Further data are required before a Bier block should be routinely recommended. It is important to note that calcium chloride should not be used in any of the techniques described above as it can cause severe tissue necrosis.

For all dermal exposures, specialized followup and wound care is indicated.

Inhalational Toxicity

Patients with symptomatic inhalational injuries can be treated with nebulized calcium gluconate; 4 mL of a 2.5% solution delivered via an asthma nebulizer.

Ingestions

In patients with intentional ingestions of HF, gastrointestinal decontamination poses a significant dilemma. Although placement of a nasogastric tube to perform gastric lavage in these patients is associated with risks to the patient, rapid decontamination may be life-saving. Consequently, gastric emptying via a nasogastric tube should be considered unless significant emesis has occurred. Healthcare providers should exercise extreme caution during this procedure because dermal or inhalational exposures to the clinicians may occur if appropriate protection is not employed. A solution of calcium or magnesium salts should be administered orally as soon as possible to prevent HF penetration and to provide an alternative source of cations for the electronegative fluoride ions. Experimentally, calcium may be better than magnesium in reducing the bioavailability of fluoride. Magnesium citrate, magnesium sulfate, or any of the calcium solutions can be administered orally to prevent absorption.

Ophthalmic Toxicity

Patients with ophthalmic exposures should have each eye irrigated with 1 L of 0.9% NaCl solution, lactated Ringer solution, or water. Repetitive or prolonged irrigation appears to worsen outcome. A complete ophthalmic examination should be performed after the patient is deemed stable, and an ophthalmology consultation should be obtained. Although some authors recommend the instillation of 1% calcium gluconate eyedrops, this therapy has not been adequately studied and routine use is not indicated at this time.

Systemic Toxicity

If there is a clinical suspicion of severe systemic toxicity, then the immediate intravenous administration of calcium and magnesium salts is recommended. In general, calcium gluconate is preferred over calcium chloride because of the risks associated with extravasation. Patients can require many grams of calcium to treat severe HF toxicity. Intravenous magnesium can be administered to adults as 20 mL of a 20% solution (4 g) over 20 minutes. Local therapy should always be used in conjunction with intravenous therapy to limit dermal or gastrointestinal absorption. Sodium bicarbonate, dextrose, and insulin should also be used if hyperkalemia is present. Therapy should be guided by rapid determinations of serum electrolytes and ECG findings.

Because fluoride ions are eliminated renally, hemodialysis may be considered in patients with severe HF poisoning if renal function is compromised. There are several reported cases of successful clearance of fluoride ions via hemodialysis with one case also using continuous venovenous hemodialysis (CVVHD). As the reported clearance rate did not significantly differ from normally functioning kidneys, it is unclear whether hemodialysis alters outcome in patients with normal renal function.

The antidysrhythmics quinidine and amiodarone are efficacious in animal models of HF poisoning, but this benefit has not been confirmed in humans. Further studies are required before a specific antidysrhythmic can be recommended.

Calcium

Calcium is essential in maintaining the normal function of the heart, vascular smooth muscle, skeletal system, and nervous system. It is vital in enzymatic reactions, in neurohormonal transmission, and in the maintenance of cellular integrity. There are multiple toxicologic indications for calcium administration. Dosing and route may vary based on these indications.

CALCIUM CHANNEL BLOCKERS

Calcium enters cells in numerous ways; of these only the voltage-dependent L-type channels in cardiac and smooth muscles are inhibited by the calcium channel blockers (CCBs) available in the United States. Because CCBs do not alter either receptor-operated channels or the release of calcium from intracellular stores, the serum calcium concentration remains normal both in therapeutic dose and in overdose.

Intravenous administration of calcium improves cardiac output secondary to an increase in inotropy, whereas heart rate and cardiac conduction are only affected when larger doses of calcium are given. Calcium should be administered to symptomatic patients with CCB overdoses. Unfortunately, the sickest patients respond inadequately, and require additional measures.

The dose of calcium needed to treat patients with CCB overdose is unknown. The customary approach is to administer an initial intravenous dose of 3 g of calcium gluconate (30 mL of 10% calcium gluconate) or 1 g of calcium chloride (10 mL of 10% calcium chloride) in adults. This dose may be repeated every several minutes, as needed. One author used a total of 12.5 g calcium gluconate over 28 minutes in an adult. Several authors have successfully treated patients with 18–30 g of calcium gluconate either by bolus dose or infusion without adverse effects. Children should receive 60 mg/kg (0.6 mL/kg of 10% calcium gluconate), titrating to the adult dose, if needed.

The administration of calcium to a patient with cardioactive steroid toxicity may result in death. In the event of concurrent overdose with both a cardioactive steroid and a calcium channel blocker, the early use of digoxin-specific antibody fragments should enable the subsequent use of calcium.

ETHYLENE GLYCOL

Ethylene glycol poisoning (Chap. 103) results in the generation of oxalic acid, which complexes with calcium and subsequently precipitates in the kidneys, brain, and elsewhere with resultant significant hypocalcemia. Intravenous calcium should be administered in the customary doses (as above) to patients based on frequent clinical and serum calcium monitoring.

HYDROFLUORIC ACID AND FLUORIDE AND BIFLUORIDE SALTS

Soluble salts of fluoride and bifluoride (eg, sodium, potassium and ammonium) have all of the toxicity associated with hydrofluoric acid and should be managed accordingly. Contact with hydrofluoric acid can result in severe burns and death. Following hydrofluoric acid exposure, calcium gluconate is used locally to manage cutaneous burns, and intravenously to treat systemic hypocalcemia. Experi-

mental studies demonstrate that when concentrated hydrofluoric acid burns are immediately flushed with water and then covered with 2.5% calcium gluconate gel, there is a significant reduction in burn size. In the event that the commercial preparation is inaccessible, a topical calcium gel can be prepared from calcium carbonate tablets or calcium gluconate powder or solution, and a water-soluble jelly such as K-Y Jelly (mix 3.5 g calcium gluconate powder or 25 mL of calcium gluconate 10% solution or 10 g of calcium carbonate tablets with 5 ounces of K-Y Jelly). For moderate to severe burns (generally from hydrofluoric acid concentrations greater than 10%) of the fingers and hands, an intraarterial calcium infusion may be more effective than local (or IV) therapy. Dilute 10 mL of 10% calcium gluconate solution mixed in 40–50 mL of 5% dextrose in water and infuse intraarterially into the affected extremity over 4 hours. This therapy can be repeated as necessary. Inhalational exposures should be treated with nebulized 2.5% calcium gluconate prepared by mixing 1.5 mL of 10% calcium gluconate solution with 4.5 mL of sterile water and delivered via an asthma nebulizer.

Deaths from hypocalcemia secondary to skin, gastrointestinal, and inhalational hydrofluoric acid toxicity are documented in the literature. To facilitate the delivery of maximum amounts of calcium, simultaneous administration of IV, oral, nebulized, and local calcium therapies may be required. It is also important to check for hypomagnesemia and hyperkalemia, which frequently occur.

PHOSPHATES

Inappropriate use of oral and rectal phosphates (eg, laxatives) can result in hypocalcemia, hyperphosphatemia and hyperkalemia resulting in significant morbidity and mortality. Intravenous calcium may be needed for life-threatening hypocalcemia.

HYPERMAGNESEMIA

Hypermagnesemia causes both direct and indirect depression of skeletal muscle function, resulting in neuromuscular blockade, loss of reflexes, and profound muscular paralysis. Intravenous calcium serves as a physiologic antagonist to these effects of magnesium and should be administered as detailed above.

HYPERKALEMIA

Calcium makes the membrane threshold potential less negative so that a larger stimulus is required to depolarize the cell. This stabilization antagonizes the hyperexcitability caused by modest hyperkalemia.

β-ADRENERGIC ANTAGONISTS

The negative inotropic action of β-adrenergic antagonists is related to interference with both the forward and reverse transport of calcium. In a canine model of propranolol poisoning, calcium improved mean arterial pressure, maximal left ventricular pressure change over time, and peripheral vascular resistance, but had no effect on bradycardia or QRS prolongation. Several case reports attest to the beneficial effects of calcium in β-adrenergic antagonist overdose.

BLACK WIDOW SPIDER ENVENOMATION

Envenomation by the black widow spider (*Latrodectus* spp) leads to local severe abdominal or back pain. The venom exerts its effects by opening sodium

TABLE A27–1. Calcium Salts for Intravenous Use

	Calcium Gluconate (Ca^{2+} Gluconate)	Calcium Chloride ($CaCl_2$)
10% Solution	10 mL = 1 g of Ca^{2+} gluconate 1 mL = 0.45 mEq elemental Ca^{2+}	10 mL = 1 g of $CaCl_2$ 1 mL = 1.36 mEq elemental Ca^{2+}
Adult dose	3 g (30 mL of 10% Ca^{2+} gluconate) Repeat every several minutes as necessary	1 g (10 mL of 10% $CaCl_2$) Repeat every several minutes as necessary
Pediatric dose (not to exceed the adult dose)	60 mg/kg (0.6 mL/kg) of Ca^{2+} gluconate 10% infused by slow intravenous bolus over 10–20 seconds in cardiac arrest or over 5–10 minutes in a well-perfused patient Repeat every several minutes as necessary	20 mg/kg (0.2 mL/kg) infused by slow intravenous push over 10–20 seconds in cardiac arrest or over 5–10 minutes in a hemodynamically stable patient Repeat every several minutes as necessary

channels leading to calcium influx and, the release of synaptic transmitters, such as norepinephrine and acetylcholine. Although calcium is frequently recommended, a large retrospective study demonstrated that few patients had adequate pain relief from calcium, and all but one patient also required opioids. Most research suggests that there is no role for calcium, in the management of black widow spider envenomation.

SAFETY ISSUES AND CALCIUM PREPARATIONS

The adverse effects of hypercalcemia include nausea, vomiting, constipation, hypertension if intravascular volume is maintained, polyuria, polydipsia, cognitive difficulties, hyporeflexia, coma, and enhanced sensitivity to cardioactive steroids. Under most circumstances calcium administration does not produce clinically significant hypercalcemia. However, under certain circumstances, such as life-threatening CCB overdose, some of these effects may be acceptable if continued calcium administration is otherwise beneficial.

Calcium chloride and calcium gluconate are commonly used (Table A27–1). Calcium chloride is an acidifying salt and is extremely irritating to tissue. It should never be given intramuscularly, subcutaneously, or perivascularly. Consequently, calcium gluconate is selected in almost all clinical situations. Equivalent doses of calcium chloride and calcium gluconate produce similar serum ionized calcium measurements, with peaks occurring within 30 seconds and accompanied by similar measured hemodynamic values.

Intravenous calcium must be administered slowly, at a rate not exceeding 0.7–1.8 mEq/min or one 10-mL vial of calcium chloride over 10 minutes in adults. More rapid administration may lead to vasodilation, hypotension, bradycardia, dysrhythmias, syncope, and cardiac arrest.

102 Hydrocarbons

There are numerous consumer and household applications of petroleum distillates as paint thinners, furniture polish, lamp oils, and lubricants (Table 102–1). While *hydrocarbon compounds* (HCs) represent chemically diverse substances, they are related primarily by the ways in which they are used. This chapter highlights the toxicology of individual hydrocarbons when they are commercially available in purified form, or when individual compounds present unique toxicologic issues.

CHEMISTRY

A *hydrocarbon* is an organic compound made up primarily of carbon and hydrogen atoms, typically ranging in length from 1–60 carbon atoms. This definition includes products derived from plants (pine oil, vegetable oil), animal fats (cod liver oil), natural gas, petroleum, and coal tar. There are two basic types of hydrocarbon molecules—*aliphatic* (straight or branched chains) and *cyclic* (closed ring)—each with its own subclasses. *Solvents* are a heterogenous class of chemical compounds used to dissolve and to provide a vehicle for delivery of other chemical substances. Specifically named solvents (Stoddard solvent, white naphtha, ligroin) represent mixtures of hydrocarbon compounds, emanating from a common distillation fraction.

The physical properties of hydrocarbons vary by the number of carbon atoms and molecular structure (Table 102–2). Unsubstituted, aliphatic hydrocarbons containing up to 4 carbons are gaseous at room temperature, 5–19 carbon molecules are liquid, and longer-chain molecules tend to be tars or solids. Most commercial hydrocarbon products are variable mixtures of individual hydrocarbon compounds, such as gasoline, which contains alkanes, alkenes, naphthenes, and aromatic hydrocarbons, predominantly 5–10 carbon molecules in size. Most commercially available gasolines blend up to eight component fractions, and more than 1500 individual compounds may be present in commercial grades.

HISTORY AND EPIDEMIOLOGY

Today, the principal commercial source of hydrocarbons involves distillation of crude oil. Occupations at risk for solvent exposure include petrochemical workers, plastics and rubber workers, printers, laboratory workers, painters, and hazardous waste workers. But exposures are ubiquitous in many occupations, and even in everyday life. In fact, the Occupational Safety and Health Administration estimates that nearly 238,000 American workers are exposed annually to significant concentrations of benzene alone. Three populations appear to be at risk for hydrocarbon-related illness: children with unintentional exposures—often ingestions; workers with occupational exposures—often dermal and inhalational; and adolescents/young adults who intentionally abuse solvents through inhalation.

PHARMACOLOGY

The acute toxicity of inhaled hydrocarbon vapor manifests principally through depression of consciousness. The acute central nervous system (CNS) toxicity

TABLE 102–1. Household Products Containing Hydrocarbons

Adhesives (glues)	Mothballs
Baby oil	Motor oils
Car waxes	Naphtha
Cod liver oil	Paint removers
Contact cement	Paint thinners
Furniture polishes	Paraffin
Furniture refinishers	Paste waxes
Gasoline	Petroleum jelly
Home heating fuel	Pine oils
Kerosene	Plastic cement
Kitchen waxes	Solvents
Lacquers	Stain removers
Laxatives	Sterno fuel
Lighter fluids	Stoddard solvent
Liquid solder	Turpentine
Liquid steel	Typewriter correction fluids
Mineral oil	Varnish removers
Mineral seal oil	Wax
Mineral spirits	

of solvent vapors parallels the pharmacology of an inhaled general anesthetic (Chap. 65). The concentration of a volatile anesthetic that will produce loss of nociception in 50% of patients is defined as the minimum alveolar concentration (MAC) required to induce anesthesia. The property of an inhaled anesthetic which correlates most closely with its ability to extinguish nociception is its lipid solubility. The Meyer-Overton hypothesis, proposed more than 100 years ago, implies that an anesthetic agent dissolves into some crucial lipid compartment of the CNS, causing inhibition of neuronal transmission. At least some hydrocarbons also have specific cellular sites of action within the CNS. Toluene inhibits neurotransmission at glutamate *N*-methyl-D-aspartate receptors. Toluene and 1,1,1-trichloroethane (TCE) enhance glycine receptor function.

TOXICOKINETICS

Inhalation is a major route of exposure for most volatile hydrocarbons. Human toxicokinetic data are lacking for most hydrocarbons, and much of our understanding of the kinetics of this large family of chemicals comes from animal studies. Hydrocarbons are variably absorbed through ingestion, inhalation, or dermal routes of exposure, depending on their structure and chemical properties. Partition coefficients, in particular, are useful predictors of the rate and extent of the absorption and distribution of hydrocarbons into tissues as the higher the value the greater the potential for redistribution. The blood-to-air and tissue-to-air or tissue-to-blood coefficients directly relate to the pulmonary uptake and distribution of hydrocarbons. Table 102–3 presents the partition coefficients for commonly encountered hydrocarbons.

Absorption of aliphatic hydrocarbons through ingestion is inversely related to molecular weight, ranging from complete absorption at lower molecular weights, to approximately 60% for C-14 hydrocarbons, 5% for C-28 hydrocarbons, and essentially no absorption for aliphatic hydrocarbons with >32 carbons. Oral absorption of aromatic hydrocarbons with between 5 and 9 carbons

TABLE 102–2. Physical Properties of Common Hydrocarbons

Compound	Carbon Atoms/ Formula	Common Uses	Boiling Point °F (°C)	Viscosity (SSU)[a]
Aliphatics				
Gasoline	4–10	Motor vehicle fuel	86–410 (30–210)	30
Naphtha	8–12	Charcoal lighter fluid	212–392 (100–200)	29
Kerosene	5–15	Heating fuel	392–572 (200–300)	35
Turpentine	$C_{10}H_{16}$	Paint thinner	311 (155)	33
Mineral spirits	9–12	Paint and varnish thinner	230–392 (110–200)	30–35
Mineral seal oil	13–17	Furniture polish	572–932 (300–500)	30–35
Heavy fuel oil	20–45	Heating oil	617–1004 (325–540)	>450
Aromatics				
Benzene	C_6H_6	Solvent, reagent, gasoline additive	176 (80)	31
Toluene	C_7H_8	Solvent, spray paint solvent	231.8 (111)	28
Xylene	C_8H_{10}	Solvent, paint thinner, reagent	291.2 (144) (*o*), 282.2 (139) (*m*), 280.4 (138) (*p*)	28
Halogenated				
Methylene chloride	CH_2Cl_2	Solvent, paint stripper, propellant	104 (40)	27
Carbon tetrachloride	CCl_4	Solvent, propellant, refrigerant	170.6 (77)	30
Trichloroethylene	$HClC = CCl_2$	Degreaser, spot remover	188.6 (87)	27
Tetrachloroethylene	$Cl_2C = CCl_2$	Dry cleaning solvent, chemical intermediate	249.8 (121)	28

[a]Direct values for kinematic viscosity in Saybolt seconds universal (SSU) were not available for the following compounds: naphtha, xylene, methylene chloride, carbon tetrachloride, trichloroethylene, perchloroethylene, and toluene. SSU was calculated by converting from available measurements in centipoise viscosity and/or centistokes viscosity using the following conversions: the value in centistokes is estimated by dividing centipoise by density at 68°F (20°C); SSU is approximated from centistokes using $y = 3.2533x + 26.08$ ($R^2 = 0.9998$). Centipoise viscosity for naphtha was estimated from the value for butylbenzene. Centipoise viscosity for xylene is the average of *o*-, *m*-, and *p*-xylene.

TABLE 102–3. Kinetic Parameters of Select Hydrocarbons

	Partition Coefficients		$t_{1/2}$			
	Blood/ Air	Fat/ Air	α	β	Elimination	Relevant Metabolites
Aliphatics						
n-Hexane	2.29[a]	159[a]	11 min	99 min	10–20% exhaled; liver metabolism by CYP	2-Hexanol, 2, 5-hexanedione, γ-valerolactone
Paraffin/tar	Not absorbed or metabolized					
Aromatics						
Benzene	8.19	499[a]	8 h	90 h	12% exhaled; liver metabolism to phenol	Phenol, catechol, hydroquinone, and conjugates
Toluene	18.0[a]	1021[a]	4–5 h	15–72 h	Extensive liver extraction and metabolism	80% metabolized to benzyl alcohol; 70% renally excreted as hippuric acid
o-Xylene	34.9	1877[a]	30–60 min	20–30 h	Liver CYP oxidation	Toluic acid, methyl hippuric acid
Halogenated						
Methylene chloride	8.94	120[a]	Apparent $t_{1/2}$ of COHb 13 h	40 min	92% exhaled unchanged. Low doses metabolized; high doses exhaled. Two liver metabolic pathways	(a) CYP 2E1 to CO and CO_2 (b) Glutathione transferase to CO_2, formaldehyde, formic acid
Carbon tetrachloride	2.73	359[a]	84–91 min[a]	91–496 min[a]	Liver CYP, some lung exhalation (dose-dependent)	Trichloromethyl radical, trichloromethyl peroxy radical, phosgene
TCE	8.11	554[a]	3 h	30 h	Liver CYP—epoxide intermediate; trichloroethanol is glucuronidated and excreted	Chloral hydrate, trichloroethanol, trichloroacetic acid
1,1,1-Trichloroethane	2.53	263[a]	44 min	53 h	91% exhaled; liver CYP	Trichloroacetic acid, trichloroethanol
Tetrachloroethylene	10.3	1638[a]	160 min	33 h	80% exhaled; liver CYP	Trichloroacetic acid, trichloroethanol

[a]Fat/blood partition coefficient is obtained by dividing the fat/air coefficient by the blood/air coefficient. As determined in rat models. All coefficients are determined at 98.6°F (37°C).

ranges from 80–97%. Oral absorption data for aromatic hydrocarbons with greater than 9 carbons is limited. While the skin is a common area of contact with solvents, for most hydrocarbons the dose received from dermal exposure is a small fraction of the dose received through other routes, such as inhalation. However, with massive exposure, (eg, whole-body immersion), dermal absorption may contribute significantly to toxicity.

Once absorbed into the central compartment, hydrocarbons are distributed to target and storage organs based on their tissue-to-blood partition coefficients, and on the rate of perfusion of the tissue with blood. Table 102–3 lists the distribution half-lives of selected hydrocarbons.

Hydrocarbons can be eliminated from the body unchanged, for example, through expired air, or can be metabolized to more polar compounds, which are then excreted through urine or bile. Table 102–3 lists the blood elimination half-lives (for first-order elimination processes) and metabolites of selected hydrocarbons. Some hydrocarbons are metabolized to toxic compounds, as discussed below.

PATHOPHYSIOLOGY

A number of other animal models employing gastric instillation of hydrocarbon demonstrated lack of pulmonary toxicity when aspiration did not occur. It is currently held that aspiration is the main route of injury from ingested hydrocarbons. The mechanism of pulmonary injury, however, is incompletely understood. Pathologic changes include interstitial inflammation, polymorphonuclear exudates, intraalveolar edema and hemorrhage, hyperemia, bronchial and bronchiolar necrosis, and vascular thrombosis. These changes most likely reflect both direct toxicity to pulmonary tissue and disruption of the lipid surfactant layer.

Several factors are associated with pulmonary toxicity after hydrocarbon ingestion. These include specific physical properties of the hydrocarbon ingested (Table 102–2) the volume ingested and the occurrence of vomiting. The properties of *viscosity*, *surface tension*, and *volatility* of a particular hydrocarbon are the main determinants of its aspiration potential. *Viscosity* is the measurement of the resistance of a fluid to flow. Substances with low viscosities (Saybolt seconds universal [SSU] <60: turpentine, gasoline, naphtha) are associated with a higher tendency for aspiration in animal models. *Surface tension* is a cohesive force generated between molecules. This influences adherence of a liquid compound along a surface ("its inability to creep"). The lower the surface tension, the higher the aspiration risk. *Volatility* is the tendency for a liquid to become a gas. It is not clear which of the physical properties of the hydrocarbon is most important in predicting toxicity, but most authorities suggest that viscosity is the single most important physical property, while vomiting, coughing, or choking are the most important pieces of clinical information.

Intravenous (IV) and subcutaneous injection of hydrocarbons are reported. Severe hydrocarbon pneumonitis may occur following intravenous exposure. The clinical course after IV hydrocarbon injection is comparable to that of hydrocarbon aspiration.

Cardiac

Exposure to hydrocarbons by any route may cause cardiotoxicity. Halogenated hydrocarbons and benzene are the compounds most frequently implicated, al-

though toluene and gasoline may also induce dysrhythmias. Dysrhythmia-induced sudden death, termed the "sudden sniffing death syndrome," is well-described after inhalation of chlorinated hydrocarbons, but also for aromatic compounds. Classically, sudden death in the setting of hydrocarbon exposure follows an episode of significant exertion. The mechanism of dysrhythmia induction appears to be endogenous catecholamine mediated extrasystoles occurring in the setting of altered repolarization, manifested by QTc prolongation (Chap. 23).

Central Nervous System

The specific mechanism of CNS depression from hydrocarbon poisoning is unclear. It is enticing to propose that specific channel inactivation or stimulation of inhibitory channels is responsible. However, to date, no unifying theory or evidentiary support for specific receptor binding explains the acute CNS impairment. In cases of hydrocarbon aspiration, hypoxia from pulmonary damage may contribute to the CNS depression. The CNS toxicity following chronic toluene exposure illustrates the ability of some hydrocarbons to produce CNS pathology. Prolonged, moderate to heavy exposure to hydrocarbons, as seen in volatile solvent abuse (Chap. 79), can lead to irreversible CNS damage. The primary pathologic process is white matter degeneration, or leukoencephalopathy.

Peripheral Nervous System

Peripheral neuropathy is well described following occupational exposure to *n*-hexane or methyl-*n*-butyl ketone (MBK). This axonopathy results from a metabolic intermediate—2,5-hexanedione—common to both hexane and MBK. Cranial and peripheral neuropathies are reported after acute and chronic exposure to TCE, which appears to induce a myelinopathy.

Hepatic

Chlorinated hydrocarbons are particularly hepatotoxic. In most cases, this occurs via phase I activation to a reactive intermediate (Chap. 14). Hepatic injury, manifested as aminotransferase elevation and hepatomegaly, is usually reversible, except following massive exposures.

Dermal

Most hydrocarbon solvents cause nonspecific irritation of the skin and mucous membranes. Repeated, prolonged contact can dry and crack the skin. The mechanism of dermal injury appears to be defatting of the lipid layer of the stratum corneum.

CLINICAL MANIFESTATIONS

Most patients who develop pulmonary toxicity after hydrocarbon ingestion will have an episode of coughing, gagging, and choking. This occurs shortly after ingestion, usually within 30 minutes, and is presumptive evidence of aspiration. Manifestations include rales, rhonchi, bronchospasm, tachypnea, hypoxia, hemoptysis, acute lung injury (hemorrhagic or nonhemorrhagic), and signs of respiratory distress. Clinical findings often worsen over several days but typically resolve within 5–7 days. Radiographic evidence of pneu-

monitis develops as early as 15 minutes or as late as 24 hours after exposure. Chest radiographs performed immediately on initial presentation are not useful in predicting infiltrates in either symptomatic or asymptomatic patients. Radiographic changes often progress over several days, typically reaching a maximum at 5–7 days, with resolution over several weeks. Radiographic resolution does not correlate with clinical improvement and usually lags behind by several days to weeks.

Cardiac

The most worrisome cardiotoxicity associated with hydrocarbon exposure is that of myocardial sensitization and dysrhythmias. Atrial fibrillation, ventricular fibrillation, and sudden cardiac death are reported.

Central Nervous System

Transient CNS excitation may occur initially after acute hydrocarbon inhalation or ingestion. More commonly, CNS depression or general anesthesia occurs, and may be profound. Coma and seizures are reported in 1–3% of cases. Chronic occupational exposure or volatile substance use may lead to a chronic neurobehavioral syndrome. Clinical features include ataxia, spasticity, dysarthria, and dementia, consistent with a leukoencephalopathy.

Peripheral Nervous System

Peripheral neuropathy after exposure to *n*-hexane, MBK, and possibly to toluene results from axonopathy. Symptoms begin in the distal extremities and progress proximally (a classic "dying-back" neuropathy). Trichloroethylene is associated with trigeminal neuralgia. Some evidence suggests that decomposition products or impurities in TCE may be responsible for cranial neuropathy.

Gastrointestinal

Hydrocarbons are irritants to the gastrointestinal mucous membranes. Nausea and vomiting are common after ingestion. As discussed earlier, vomiting may be associated with increased risk of pulmonary toxicity.

Hepatic

Hepatic injury may occur after exposure to halogenated hydrocarbons, particularly carbon tetrachloride. Carbon tetrachloride can produce fatal centrilobular necrosis by inhalational, oral, or dermal exposure. Vinyl chloride is a known liver carcinogen. Jaundice, right upper quadrant pain, and encephalopathy may occur. Aminotransferase elevation typically resolves with cessation of exposure, except in extreme poisoning.

Renal

Halogenated hydrocarbons are nephrotoxic. Acute renal failure and acidosis occur in some painters and volatile substance abusers. Toluene may cause a syndrome that resembles renal tubular acidosis (see discussion below).

Hematologic

Hemolysis has been sporadically reported to occur after hydrocarbon ingestion. Benzene is directly toxic to bone marrow (see below).

Dermatologic

Contact dermatitis and blistering may progress to partial and even full thickness burns. Severity is proportional to duration of exposure. Soft-tissue injection of hydrocarbon is locally toxic, leading to necrosis. Secondary cellulitis, abscess formation, and fasciitis can occur.

HYDROCARBONS WITH SPECIFIC AND UNIQUE TOXICITY

n-Hexane

n-Hexane is a 6-carbon, simple, aliphatic constituent of some brake cleaning fluids, rubber cement, glues, spray paints, coatings, and silicones. Neurotoxicity is not related to the parent compounds, but results from a metabolic intermediate—2,5 hexanedione. Similar 5-, 6-, and 7-carbon species do not induce similar neurotoxicity, except those that are direct precursor intermediates in the metabolic pathway producing 2,5 hexanedione (Table 102–3).

Methylene Chloride

Methylene chloride is perhaps most commonly found in paint removers, but is also found in cleaning and degreasing agents, and in aerosol propellants. Like other halogenated hydrocarbons, it can rapidly induce general anesthesia by inhalation or ingestion. Unlike other hydrocarbons, methylene chloride and methylene dibromide are metabolized to carbon monoxide. Significant, delayed, and prolonged carboxyhemoglobinemia may result (Chap. 120).

Carbon Tetrachloride

Toxicity follows phase I dehalogenation of the parent compound, which produces free radicals and causes lipid peroxidation and the production of protein adducts. Localization of specific phase I hepatic enzymes in the centrilobular area of the liver results in regionalized (zone 3) centrilobular injury after CCl_4 exposure (Chap. 26). Hepatotoxicity is typically manifested as reversible aminotransferase elevation with or without hepatomegaly.

Benzene

Benzene is hematotoxic and is associated with acute hemolysis, or the delayed development of aplastic anemia and acute myelogenous leukemia.

Toluene

Toluene is readily available and abused as an inhalant. The CNS sequelae of chronic solvent inhalation are most frequently related to chronic toluene exposure (see above). Chronic toluene abuse produces a syndrome that resembles distal renal tubular acidosis (RTA) with a hyperchloremic (normal anion gap) metabolic acidosis and hypokalemia. The hypokalemia can be severe and require aggressive replacement.

DIAGNOSTIC TESTING

Laboratory and ancillary testing for hydrocarbon toxicity should be guided by available information regarding the specific agent, the route of exposure, and the best attempt at quantifying the exposure. Specific hydrocarbon con-

centrations are either unavailable or do not return in a clinically useful timeframe. Assessments of respiratory, cardiac, hepatic, renal, hematologic and neurologic status should be guided by clinical information. While early radiography is indicated in patients who are severely symptomatic the 6-hour chest radiograph has strong predictive value.

MANAGEMENT

Because hydrocarbons are a diverse family of compounds with a wide spectrum of toxicities identification of the specific type, route, and amount of hydrocarbon exposure is essential to effective management.

Decontamination of the skin should have high priority in massive hydrocarbon exposures, particularly those exposures involving highly toxic hydrocarbons. Water may be ineffective to decontaminate most hydrocarbons, but early decontamination with soap and water may be adequate. Gastric decontamination is of no benefit and potentially detrimental following ingestion of a hydrocarbon where the primary toxicity is expected to be pulmonary. However when severe systemic toxicity is expected as may be the case when the hydrocarbon is used to solubilize a potent xenobiotic, gastric emptying should be considered (Table 102–4). Activated charcoal (AC) has limited ability to decrease gastrointestinal absorption of hydrocarbons and may distend the stomach and predispose patients to vomiting and aspiration. The use of AC is only justified in patients with significant mixed overdoses.

Abnormal lung auscultation, fever, leukocytosis, and abnormal radiographic findings are the initial manifestations of both bacterial pneumonia and hydrocarbon pneumonitis. Decisions regarding antibiotic use are complex. As a result, antibiotics are frequently administered in the setting of hydrocarbon pneumonitis, despite the absence of experimental evidence of benefit. Ideally, sputum cultures should direct antibiotic use. Similarly, animal models and two controlled human trials failed to show a benefit from corticosteroid administration. Likewise, no evidence supports routine administration of surfactant.

Respiratory distress requiring mechanical ventilation may be associated with a large ventilation–perfusion mismatch. The use of positive end-expiratory pressure (PEEP) in this setting is often beneficial. However, very high levels of PEEP may be required with subsequent increased risk of barotrauma. Extracorporeal membrane oxygenation (ECMO) appears beneficial when more tradition means of oxygenation fail.

TABLE 102–4. Gastric Emptying for Hydrocarbon Ingestion

Contraindications
• Occurrence of spontaneous vomiting
• Asymptomatic initially and at initial medical evaluation
Indications
• A hydrocarbon with inherent systemic toxicity (CHAMP)
C: camphor
H: halogenated hydrocarbons
A: aromatic hydrocarbons
M: hydrocarbons containing metals
P: hydrocarbons containing pesticides

Management of dysrhythmias associated with hydrocarbon toxicity should include consideration of electrolyte and acid–base abnormalities (eg, hypokalemia and acidosis from toluene), hypoxemia, hypotension, and hypothermia. Ventricular fibrillation poses a specific concern, as common resuscitation algorithms recommend epinephrine administration to treat this rhythm. If it is ascertained that the dysrhythmia emanates from myocardial sensitization by a hydrocarbon solvent, catecholamines should be avoided. In this setting, lidocaine has been used successfully, as has β-adrenergic antagonism.

In the past, hospital admission was routinely recommended for patients who had ingested hydrocarbons, because of the concern over possible delayed symptom onset and progression of toxicity. Current evidence suggests that a patient who is asymptomatic after a 6-hour observation period *and* who has a normal 6-hour chest radiograph is at an exceedingly low risk of consequential deterioration. Those patients who have clinical evidence of toxicity and most individuals with intentional ingestions should be hospitalized. Care should be individualized for patients who are asymptomatic but who have radiographic evidence of hydrocarbon pneumonitis.

103 Toxic Alcohols

CHEMISTRY

Alcohols are hydrocarbons that contain on *hydroxyl* (OH) group. The term *toxic alcohols* traditionally refers to alcohols other than ethanol. The most common toxic alcohols encountered clinically are methanol, ethylene glycol, and isopropanol. *Primary* alcohols, such as methanol and ethanol, contain a hydroxyl group on the end of the molecule (the *terminal* carbon), whereas *secondary* alcohols, such as isopropanol, contain hydroxyl groups bound to nonterminal carbons. Glycol ethers are glycols with a hydrocarbon chain bound to one or more of the hydroxyl groups (forming the basic structure $R_1O\text{-}CH_2\text{-}CH_2\text{-}O\text{-}R_2$ or $R_1O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}OR_2$).

HISTORY AND EPIDEMIOLOGY

Methanol-containing consumer products that are commonly encountered include model airplane fuel, windshield washer fluid, solid cooking fuel, photocopying fluid, perfumes, and gas line antifreeze ("dry gas"). Methanol is also used as a solvent by itself or as an adulterant in "denatured" alcohol. Most reported cases of methanol poisoning in the United States involve ingestions of one of these products, with more than 60% caused by windshield washer fluid, according to one review. Sporadic epidemics of mass methanol poisoning result from tainted fermented beverages. Ethylene glycol is widely used as an engine coolant. Isopropanol is primarily available as rubbing alcohol, typically as a 70% solution. Glycol ethers are responsible for many poisoning epidemics in the 20th century. Diethylene glycol was substituted for propylene glycol as a medical diluent. The first such epidemic involved an elixir of sulfanilamide in the United States, with subsequent epidemics in India, Nigeria, Bangladesh, Haiti and, most recently, Panama.

TOXICOKINETICS AND TOXICODYNAMICS

Alcohols are rapidly absorbed after ingestion, but not completely bioavailable because of metabolism by gastric alcohol dehydrogenase (ADH) and first-pass metabolism in the liver. Methanol may also be absorbed in significant amounts by inhalation. Ethylene glycol and the glycol ethers have low volatility and are not reported to cause poisoning by inhalation. Most alcohols have some dermal absorption. Isopropanol, methanol, and the glycol ethers penetrate the skin much better than ethylene glycol. Once absorbed, alcohols are rapidly distributed to total-body water.

Without intervention, toxic alcohols are eliminated primarily through successive metabolism by ADH and aldehyde dehydrogenase (ALDH) (Figs. 103–1, 103–2, and 103–3; also shown are alternate minor metabolic pathways for methanol and ethylene glycol). Methanol and ethylene glycol also may be eliminated from the body as unchanged parent compounds. When renal function is normal, ethylene glycol is slowly cleared by the kidneys, with a half-life of approximately 11–18 hours. Methanol does not have significant renal elimination, and is cleared much more slowly than is ethylene glycol as a vapor in expired air (half-life 30–54 hours).

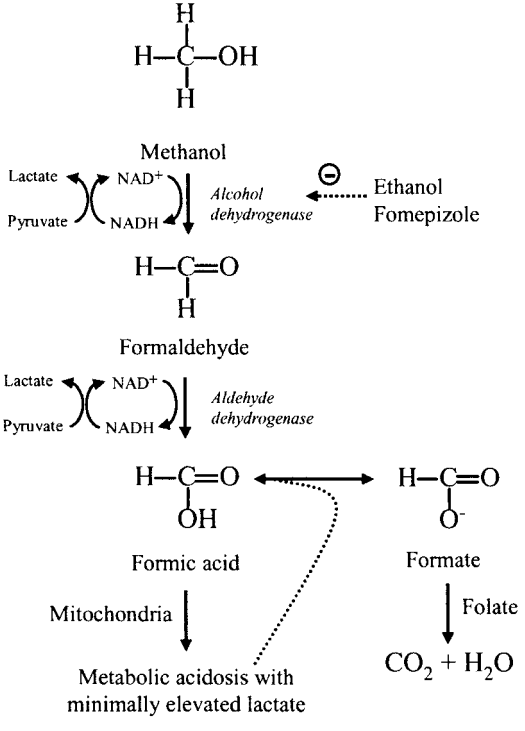

FIG. 103–1. Major pathways of methanol metabolism. Metabolic acidosis worsens toxicity by shifting the equilibrium to favor the more toxic formic acid.

CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY

CNS Effects

All alcohols may cause inebriation, depending on the dose. Higher-molecular-weight alcohols are more intoxicating than lower-molecular-weight alcohols (eg, isopropanol ≈ ethylene glycol > ethanol > methanol). The absence of apparent inebriation does not exclude toxic alcohol ingestion.

Metabolic Acidosis

Metabolic acidosis with an elevated anion gap is a hallmark of toxic alcohol poisoning. In methanol poisoning, formic acid is responsible for the acidosis (lactate may also contribute), whereas in ethylene glycol poisoning, glycolic acid is the primary acid responsible for the acidosis. Isopropanol is an exception in that it is metabolized to acetone, a ketone that cannot be further oxidized to an acid.

Specific End-Organ Effects

Methanol causes visual impairment ranging from blurry or hazy vision or defects in color vision, to "snowfield vision" or total blindness in severe poison-

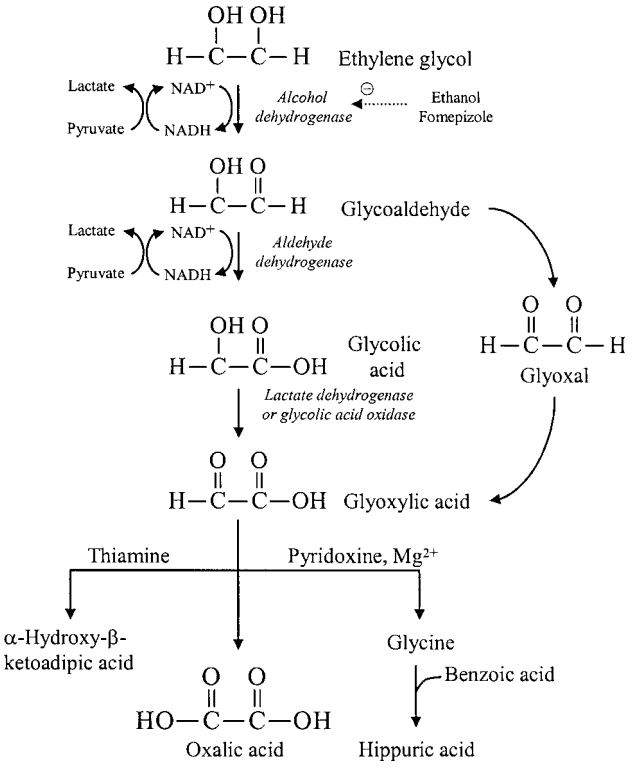

FIG. 103–2. Pathways of ethylene glycol metabolism. Thiamine and pyridoxine enhance formation of nontoxic metabolites.

ing. The formic acid metabolite of methanol is a mitochondrial toxin, which inhibits cytochrome oxidase (much like cyanide) and thereby interferes with oxidative phosphorylation. Neurons in the basal ganglia appear to be similarly susceptible to this toxicity; bilateral basal ganglia lesions (particularly

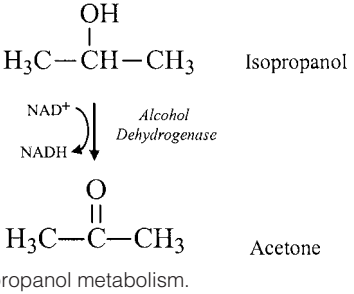

FIG. 103–3. Isopropanol metabolism.

putamen and, less commonly, caudate nucleus) characteristically are visualized on cerebral computerized tomography or magnetic resonance imaging after methanol poisoning. Rarely, pancreatitis, myoglobinuria, and renal failure also are associated with severe methanol poisoning.

The most prominent end-organ effect of ethylene glycol is nephrotoxicity. The oxalic acid metabolite forms a complex with calcium to precipitate as crystals in the renal tubules, leading to acute renal failure. Direct tubular toxicity may also occur. Other effects include hypocalcemia and QTc prolongation with dysrhythmias and cranial nerve abnormalities.

Hemorrhagic gastritis also is associated with isopropyl alcohol intoxication.

DIAGNOSTIC TESTING

Toxic Alcohol Concentrations

Actual serum methanol, ethylene glycol, and isopropanol concentrations are the ideal tests to perform when toxic alcohol poisoning is suspected. However, they are not available in most hospital laboratories on a 24-hour basis, if at all. Patients presenting late after ingestion may already have metabolized all of the parent compound to toxic metabolites, and thus may have low or no measurable toxic alcohol concentrations. Consequently, a low or undetectable toxic alcohol concentration must be interpreted within the context of the history and other clinical data.

Because of the problems with obtaining and interpreting actual serum concentrations, many surrogate markers have been used to assess the patient with suspected toxic alcohol poisoning. Tests like osmol gaps, urine fluorescence, and urine for crystals all have poor sensitivity and specificity and are rarely of value. The initial laboratory evaluation should include serum electrolytes (including calcium), blood urea nitrogen, and serum creatinine. An arterial or venous blood gas analysis with a lactate concentration is also helpful in the initial evaluation of ill-appearing patients. It should be noted that some rapid analyzers misinterpret glycolate as lactate, leading to false-positive results.

A serum ethanol concentration is an important part of the assessment of the patient with suspected toxic alcohol poisoning. Because ethanol is the preferred substrate of ADH, a significant concentration is protective. Thus in most circumstances, if the ethanol concentration is elevated (especially near 100 mg/dL), acidosis is unlikely to have resulted from a toxic alcohol. The exception is ingestion of ethanol several hours after ingestion of a toxic alcohol.

MANAGEMENT

Immediate resuscitation of critically ill patients starts with management of the airway, breathing, and circulation. Hypotension should be treated initially with fluid resuscitation. Gastrointestinal decontamination is rarely, if ever, indicated for toxic alcohols because of their rapid absorption and limited binding to activated charcoal.

Alcohol Dehydrogenase Inhibition

The most important part of the initial management of patients with known or suspected toxic alcohol poisoning (after initial resuscitation) is blockade of ADH. Although hemodialysis should be anticipated in all cases, in some cases, ADH blockade may be the only therapy needed.

Either ethanol or fomepizole may be used to block ADH (see Antidotes in Brief: Ethanol and Antidotes in Brief: Fomepizole). Although these two antidotes appear equally efficacious and fomepizole is much easier to use, it is also much more expensive. The dose of fomepizole is 15 mg/kg intravenously as an initial loading dose followed by 10 mg/kg every 12 hours. After 48 hours of therapy, fomepizole induces its own metabolism, so the dose must be increased to 15 mg/kg every 12 hours. Ethanol must be given orally or intravenously to maintain a serum concentration of approximately 100 mg/dL (see Antidotes in Brief: Ethanol for specific dosing instructions).

Any patient with a reasonable history of methanol or ethylene glycol ingestion should be treated empirically until the definitive diagnosis is established. In addition, treatment should be considered for any patient with an anion gap acidosis without another explanation or a markedly elevated osmol gap. Once concentrations are available, therapy should be continued until the serum concentration is below 25 mg/dL.

Hemodialysis

The definitive therapy for patients significantly poisoned by toxic alcohols is hemodialysis. Hemodialysis clears both the alcohols and their toxic metabolites from the blood, and corrects the acid–base status disorder. The indications for hemodialysis are somewhat controversial. Patients with end-organ toxicity or severe acidosis require ADH blockade and emergent hemodialysis. Patients with ethylene glycol poisoning who have minimal signs of toxicity and normal renal function can be managed with ADH blockade alone. While this approach may be applicable to similar patients with methanol poisoning, the relatively long half-life of methanol in the setting of ADH blockade may make hemodialysis a more practical alternative. Patients between these extremes require clinical judgment and consultation with toxicologists and nephrologists to select an optimal treatment strategy. Some patients will require multiple courses of hemodialysis to clear the toxin and or metabolites.

Although hemodialysis effectively clears isopropanol and acetone from the blood, it is rarely, if ever, indicated for this purpose. Because isopropanol does not cause a metabolic acidosis and very rarely results in significant end-organ effects, the risks of hemodialysis likely outweigh the benefits.

Adjunctive Therapy

Folate and leucovorin enhance the clearance of formate in animal models. Thiamine enhances metabolism of ethylene glycol to α-hydroxy-β-ketoadipate, and pyridoxine enhances its metabolism to glycine (and ultimately hippuric acid). While all of these modalities offer theoretical advantages, they have yet to be proven to change the outcome in humans. Because of the safety of vitamin supplementation, the potential benefits likely outweigh the risks of therapy. Dosing regimens are outlined in Antidotes in Brief: Leucovorin (Folinic Acid) and Folic Acid.

Formate (dissociated formic acid) is much less toxic than the undissociated formic acid, probably because undissociated formic acid has a much higher affinity for cytochrome oxidase in the mitochondria, the ultimate target site for toxicity. In addition, the undissociated form is better able to diffuse into target tissues. Alkalinization with a bicarbonate infusion shifts the equilibrium to favor the less toxic, dissociated form and enhances formate clearance in the urine by ion trapping. Additionally, alkalinization may be necessary to restore pH to a functional level. A blood pH greater than 7.20 is a reasonable end point.

OTHER ALCOHOLS

Propylene Glycol

Propylene glycol is commonly used as an alternative to ethylene glycol in "environmentally safe" antifreeze. It is also used as a diluent for many pharmaceuticals (such as phenytoin and lorazepam). This alcohol is successively metabolized by ADH and ALDH to lactic acid.

Benzyl Alcohol

Benzyl alcohol is used as a preservative for intravenous solutions. Although it is no longer used in neonatal medicine, it was responsible for "neonatal gasping syndrome," involving multiorgan system dysfunction, metabolic acidosis, and death because of its metabolism to benzoic acid and hippuric acid (Chap. 53 further discusses benzyl alcohol).

GLYCOL ETHERS

Diethylene Glycol

The clinical manifestations of diethylene glycol poisoning typically begin with abdominal pain, nausea, and vomiting, followed by worsening metabolic acidosis, acute renal failure, and progressive mental status depression over several days. Children with epidemic poisoning have also manifested liver failure, respiratory failure, and neurotoxicity, including seizures, optic neuritis, and paresthesia.

It is unclear whether toxicity is caused by the diethylene glycol parent compound or a metabolite. Since limited animal data suggest a survival benefit from ADH inhibition, administration of either fomepizole or ethanol should be considered; however, when available, prompt hemodialysis is preferred because of its ability to remove both the parent compound and potentially toxic metabolites.

Butoxyethanol

Most cases of butoxyethanol poisoning involve adults with intentional ingestions. In children, unintentional exposures to household glass cleaners containing butoxyethanol typically result in few adverse effects. It does not appear that metabolism to ethylene glycol occurs in humans, but this remains controversial. Clinical manifestations of acute butoxyethanol toxicity may include mental status depression, hypotension, hemolysis, nonhemolytic anemia, hematuria, hyperchloremic metabolic acidosis, mild elevation of the aminotransferases, acute renal failure, and acute lung injury.

Partly because its metabolism and mechanism of toxicity are incompletely understood, the optimal therapy for acute butoxyethanol poisoning is still controversial. Good outcomes have been reported after ethanol therapy alone and after ethanol and bicarbonate therapy with hemodialysis. At present, alcohol dehydrogenase inhibition with ethanol or fomepizole is a reasonable intervention. Hemodialysis may be considered in patients with severe acidosis.

Fomepizole

Fomepizole is a potent competitive inhibitor of alcohol dehydrogenase (ADH) that prevents the formation of toxic metabolites from ethylene glycol and methanol. Once ADH is blocked, the decision to use hemodialysis depends on how much damage has occurred to the organs of elimination and how well the body can eliminate both the parent compound and the toxic metabolites formed prior to fomepizole administration. It may also have a role in halting the disulfiram–ethanol reaction, and in limiting the toxicity from a variety of xenobiotics that rely on alcohol dehydrogenase for metabolism to toxic metabolites.

PHARMACOLOGY

In monkeys a fomepizole concentration of 9–10 μmol/L (0.74–0.8 μg/mL) is sufficient to inhibit the metabolism of methanol to formate. Although a recent study protocol using intravenous fomepizole attempted to maintain a serum fomepizole concentration above 10 μmol/L, current dosing recommendations achieve a serum concentration in excess of 100–200 μmol/L to ensure a margin of safety.

PHARMACOKINETICS

An intravenous loading dose of 15 mg/kg of fomepizole produces a mean peak concentration of 342 μmol/L (200–400 μmol/L). At 8 hours after the loading dose, the lowest fomepizole concentration reported was 105 μmol/L. The rate of elimination was determined to be zero order at 16 μmol/L/h as compared with a first-order elimination half-life of 3 hours during hemodialysis. In healthy volunteers, oral administration produces serum concentrations similar to IV fomepizole.

METHANOL

Studies in monkeys, the animal species that most closely resembles humans with regard to the metabolism of methanol, demonstrate the inhibitory effect of fomepizole in preventing the accumulation of formate. The largest human case series to date involved 11 patients who were given IV fomepizole in the approved U.S. dosing regimen. Following administration, formate concentrations fell and the pH increased.

In concentrations of about 100–200 mg/dL, methanol exhibits zero-order kinetics and is eliminated at about 8.5–9 mg/dL/h in untreated humans. Once fomepizole is administered, the elimination of methanol becomes first order and the half-life of methanol is about 54 hours. When methanol metabolism is blocked, formate is eliminated with a half-life of 235 ±83 minutes. Thus while the acidosis should resolve rapidly in most patients following fomepizole therapy, methanol concentrations will remain elevated for a substantial period of time.

ETHYLENE GLYCOL

Case reports and case series using fomepizole orally or IV with or without hemodialysis demonstrate that fomepizole is highly effective in preventing glycolate accumulation. Once metabolism is halted, renal function is essen-

tial in the elimination of ethylene glycol. With normal renal function, the half-life of ethylene glycol is about 8.6 hours. Following fomepizole administration, the half-life is about 14–17 hours in patients with normal renal function, and about 49 hours in patients with impaired renal function. In contrast to methanol, this rapid elimination of ethylene glycol implies that many patients with minimal complications and normal renal function can be treated with fomepizole alone.

SAFETY AND ADVERSE EFFECTS

Retinol dehydrogenase, which is responsible for converting retinol to retinal in the eye, is an isozyme of ADH. Studies in several animal species demonstrate that fomepizole is relatively nontoxic, with no demonstrable signs of ophthalmic toxicity. In an oral placebo-controlled, double-blind, single-dose randomized study in healthy volunteers there were no adverse effects at 10 and 20 mg/kg dosing, whereas at 50 mg/kg subjects experienced slight to moderate nausea and dizziness. The most common adverse effects reported by the manufacturer (in a total of 76 patients and 63 volunteers) were headache 12%, nausea 11%, and dizziness 7%. Other less commonly observed adverse effects include phlebitis, rash, fever, and eosinophilia. A transient elevation of aminotransferase levels is also commonly reported. Fomepizole is not approved for use in children, but has been used successfully in children who have ingested ethylene glycol and methanol. Fomepizole is listed as pregnancy category C.

DISULFIRAM AND OTHER TOXINS

Fomepizole terminates the adverse reactions resulting from the use of disulfiram and ethanol. Pretreatment was also successful in preventing the facial flushing and tachycardia typically associated with ethanol administration in ethanol-sensitive Japanese subjects.

Limited animal studies and a few case reports suggest that fomepizole may be effective in limiting the toxicity secondary to diethylene glycol, triethylene glycol and 1,3-difluoro-2-propanol. The role of fomepizole in overdoses secondary to 2-butoxyethanol (ethylene glycol monobutyl ether, butyl Cellosolve) is unclear, but fomepizole may be useful if administered within several hours of ingestion and before rapid metabolism of butoxyethanol to butoxyacetic acid occurs. Isopropanol is probably metabolized at least in part by alcohol dehydrogenase but fomepizole therapy is not indicated, as this intervention would prolong the metabolism of isopropanol to acetone.

DOSING

The loading dose of fomepizole is 15 mg/kg IV followed every 12 hours by 10 mg/kg for 4 doses. If therapy is necessary beyond 48 hours, the dose is then increased to 15 mg/kg every 12 hours for as long as necessary. Patients undergoing hemodialysis require additional doses of fomepizole to replace the amount removed during hemodialysis. The fomepizole dose must be diluted in 100 mL of 0.9% sodium chloride solution or 5% dextrose in water (D_5W) prior to IV administration and then infused over 30 minutes to avoid venous irritation and phlebosclerosis.

Therapy should be continued until the methanol or ethylene glycol is no longer present in sufficient concentrations to produce toxicity. Although these concentrations are not precisely known, usually, in the absence of end-organ

toxicity or acid–base abnormalities, concentrations less than 25 mg/dL are well tolerated.

AVAILABILITY

Fomepizole is marketed as Antizol by Orphan Medical. Temperatures of <77°F (25°C) cause the contents of the fomepizole vials to solidify. Warming reliquefies the product without adversely affecting the potency.

COMPARISON TO ETHANOL

Ethanol has been used for many years to inhibit the metabolism of methanol and ethylene glycol. With ethyl alcohol concentrations maintained at about 100 mg/dL, the half lives of elimination of methanol and ethylene glycol are comparable to fomepizole. Since both ethanol and fomepizole work by inhibiting alcohol dehydrogenase there is no reason to believe that using both agents together would be more beneficial than either alone. However, although inexpensive, ethanol has many disadvantages compared to fomepizole that include central nervous system depression; dosing difficulties; lack of ready availability of the intravenous formulation; need to closely monitor serum concentrations of ethanol; hepatitis, pancreatitis, phlebitis, and fluid and electrolyte abnormalities. Fomepizole dosing is much easier without a need for serum concentration monitoring. Thus fomepizole is preferred. Ethanol should only be used when fomepizole is not readily available.

Ethanol

Ethanol is used therapeutically as a competitive substrate to xenobiotics metabolized by alcohol dehydrogenase (ADH), thus limiting their metabolism to toxic metabolites.

AFFINITY FOR ALCOHOL DEHYDROGENASE

The dose of ethanol necessary to achieve competitive inhibition depends on the relative concentrations of the toxic alcohols and their affinity for the enzyme. In vitro evidence demonstrates that ADH has a much higher affinity for ethanol than either methanol or ethylene glycol. In experimental animals a 1:4 molar ratio of ethanol to methanol nearly completely inhibited methanol metabolism. Even less ethanol was necessary to protect against ethylene glycol. Most authors recommend maintaining a serum ethanol concentration of 100 mg/dL. This will protect against a methanol concentration of 286 mg/dL and an ethylene glycol concentration of over 546 mg/dL. When very large ingestions are suspected or concentrations exceed the values listed above, the ethanol concentration should be increased so that the molar ratio is no less than 1:4. Inhibiting the metabolism of methanol and ethylene glycol impedes the formation of toxic metabolites and prevents the development of metabolic acidosis and toxicity. After the pathway for metabolism is blocked with ethanol, renal, pulmonary, and extracorporeal routes of toxic alcohol removal become the sole mechanisms for elimination.

When alcohol dehydrogenase is blocked by ethanol, the half-life of ethylene glycol in patients with normal renal function was 17.5 hours, which was comparable to 17 hours in patients receiving fomepizole. For methanol, a half-life of 46.5 hours is reported when an appropriate dose of ethanol is given, which is comparable to the 54-hour half-life reported in methanol-poisoned patients treated with fomepizole.

PHARMACOKINETICS AND DOSING

Ethanol can be given either enterally or IV (see Tables A29–1 and A29–2). Concentrations of 20–30% (orally) and 5–10% IV are well tolerated. Intravenous administration has the advantage of complete absorption, avoidance of gastrointestinal symptoms, and ability to be administered to an unconscious or uncooperative patient. The disadvantages of IV ethanol include difficulty in obtaining and preparing an intravenous ethanol solution, the hyperosmolarity of a 5% ethanol solution (about 950 mOsm/L), the possibility of osmotic dehydration, and venous irritation. Ethanol administered enterally is rapidly absorbed and achieves peak concentrations in about 1–1.5 hours. Sufficient concentrations are generally achieved when 0.8 g/kg of ethanol is given orally over 20 minutes.

Regardless of route, the objective is to achieve and maintain a concentration of approximately 100 mg/dL of ethanol. The IV loading dose should be administered over 20–60 minutes as tolerated by the patient. The 10% ethanol concentration is preferable to the 5% concentration so as to limit the volume of fluid administered. It is also preferred over the more concentrated solutions so as to limit local venous irritation and avoid postinfusion phlebitis. Because of the free water content and significant hypertonicity of the 10% solution, the patient should be

TABLE A29–1. Intravenous Administration of 10% Ethanol

Loading Dose[c]	Volume (mL)[b] (given over 1 hour as tolerated)					
	10 kg	**15 kg**	**30 kg**	**50 kg**	**70 kg**	**100 kg**
0.8 g/kg of 10% ethanol (infused over 1 hour as tolerated)	80	120	240	400	560	800
Maintenance Dose[a]	Infusion Rate[b] (mL/h for various weights)[d]					
	10 kg	**15 kg**	**30 kg**	**50 kg**	**70 kg**	**100 kg**
Normal						
80 mg/kg/h	8	12	24	40	56	80
110 mg/kg/h	11	16	33	55	77	110
130 mg/kg/h	13	19	39	65	91	130
Chronic Alcoholic						
150 mg/kg/h	—	—	—	75	105	150
During Hemodialysis						
250 mg/kg/h	25	38	75	125	175	250
300 mg/kg/h	30	45	90	150	210	300
350 mg/kg/h	35	53	105	175	245	350

[a]Infusion to be started immediately following the loading dose. Concentrations above 10% are not recommended for IV administration. The dose schedule is based on the premise that the patient initially has a zero ethanol concentration. The aim of therapy is to maintain a serum ethanol concentration of 100–150 mg/dL, but constant monitoring of the ethanol concentration is required because of wide variations in endogenous metabolic capacity. Ethanol will be removed by hemodialysis, and the infusion rate of ethanol must be increased during hemodialysis. Prolonged ethanol administration may lead to hypoglycemia.
[b]For a 5% concentration, multiply the amount by 2.
[c]A 10% V/V concentration yields approximately 100 mg/mL.
[d]Rounded to the nearest mL.
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TABLE A29–2. Oral Administration of 20% Ethanol

Loading Dose[b]	Volume (mL)					
	10 kg	**15 kg**	**30 kg**	**50 kg**	**70 kg**	**100 kg**
0.8 g/kg of 20% ethanol, diluted in juice. May be administered orally or via nasogastric tube	40	60	120	200	280	400
Maintenance Dose[a]	mL/h for various weights[c,d]					
	10 kg	**15 kg**	**30 kg**	**50 kg**	**70 kg**	**100 kg**
Normal						
80 mg/kg/h	4	6	12	20	28	40
110 mg/kg/h	6	8	17	27	39	55
130 mg/kg/h	7	10	20	33	46	66
Chronic Alcoholic						
150 mg/kg/h	8	11	22	38	53	75
During Hemodialysis						
250 mg/kg/h	13	19	38	63	88	125
300 mg/kg/h	15	23	46	75	105	150
350 mg/kg/h	18	26	53	88	123	175

[a]Concentrations above 30% (60 proof) are not recommended for oral administration. The dose schedule is based on the premise that the patient initially has a zero ethanol level. The aim of therapy is to maintain a serum ethanol concentration of 100–150 mg/dL, but constant monitoring of the ethanol concentration is required because of wide variations in endogenous metabolic capacity. Ethanol will be removed by hemodialysis, and the dose of ethanol must be increased during hemodialysis. Prolonged ethanol administration may lead to hypoglycemia.
[b]A 20% V/V concentration yields approximately 200 mg/mL.
[c]Rounded to the nearest mL.
[d]For a 30% concentration, multiply the amount by 0.66.
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observed for hyponatremia. A separate IV infusion of 5% dextrose in water (D_5W) in 0.45% sodium chloride solution may be necessary. The loading dose of ethanol must be followed by a maintenance dose, as metabolism is rapid (see Tables A29–1 and A29–2). Additionally, because ethanol is rapidly dialyzed, the maintenance dose should be tripled during hemodialysis and concentration must be checked to assure that adequate protection is maintained.

Regardless of the route of administration, ethanol elimination varies in each individual. Frequent serum ethanol determinations should be made to ensure adequate dosing while also monitoring blood glucose and fluid and electrolyte status. Any increase in the anion gap or decrease in bicarbonate concentration implies that the ethanol dose is inadequate to achieve blockade of alcohol dehydrogenase and the ethanol dosing should be increased. Problems encountered with the administration of ethanol include further risk of central nervous system depression or ethanol-related toxicities, such as hepatitis and pancreatitis, hypoglycemia, dehydration, and fluctuating serum concentrations, and potential drug interactions, resulting in disulfiramlike reactions.

AVAILABILITY

Commercial preparations of 5% ethanol in 5% dextrose are available for IV administration. Alternatively, sterile ethanol USP (absolute ethanol) can be added to 5% dextrose to make a solution of approximately 10% ethanol concentration. A 10% solution is made by adding 55 mL (*not* 50 mL) of absolute ethanol to 500 mL of 5% dextrose, to produce a total end volume of 555 mL. If oral administration is chosen, it is important to remember that the "proof" number on the label is double the concentration; that is, 100-proof ethanol is 50% ethanol. If there will be any delay in obtaining ethanol for intravenous use, oral therapy with ethanol should be initiated immediately.

COMPARISON TO FOMEPIZOLE

Ethanol has the advantages of easy access for oral administration and low cost, whereas fomepizole does not produce central nervous system depression, is easier to dose, and does not require serum concentration monitoring. The most important disadvantage of using fomepizole is its substantial cost, which still limits its availability in many hospitals. However, given a choice, fomepizole is preferred because of all the cited advantages. Ethanol should be used only when fomepizole is unavailable.

104 Pesticides: An Overview with a Focus on Principles and Rodenticides

Pesticides are substances or mixtures of substances intended to prevent, destroy, repel, or mitigate any pest and any substance or mixture intended for use as a plant regulator, defoliant, or desiccant. "Pests" are insects, fungi, herbs, rodents, and worms.

Since 1947, the production, use, and distribution of all pesticides in the United States has been regulated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and its subsequent amendments. The Environmental Protection Agency (EPA) was given the authority to administer and enforce FIFRA regulations in 1970. Currently under FIFRA all pesticides must be registered with the EPA and are classified for either general use or restricted use by licensed or certified applicators. The EPA and the Food and Drug Administration (FDA) together establish pesticide tolerance concentrations for agricultural products and foods. Under the 1978 amendment, FIFRA allows individual states to regulate and enforce pesticide regulations and some states have now established even more stringent requirements and lower acceptable concentrations than the EPA.

The EPA also regulates pesticides under several other Acts: The Federal Environmental Pesticide Control Act, the Resource Conservation Recovery Act of 1972 (RCRA), the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA, also called the "Superfund" Act), the Toxic Substance Control Act (TSCA), the Clean Water Act, and the Safe Drinking Water Act.

Authority is granted by FIFRA to protect the health of the population. When evidence indicates that a pesticide may be a significant health hazard, one or more of the following actions may be taken: permissible workplace exposure limits may be issued; restrictions on use or application of a product may be ordered and tolerance concentrations for pesticide residues on food stuffs or water contamination may be set; a product may be removed from sale; or its registration may be cancelled.

Table 104–1 summarizes the EPA's toxicity classifications; the significance of oral LD_{50}'s (median lethal dose for 50% of test subjects) is used to classify rodenticides below. The remainder of this chapter deals with the clinical problems posed by rodenticide poisoning. Some of the more prominent rodenticides are discussed individually in Chaps. 104 through 108; others are discussed in Chaps. 85 (Arsenic) and 96 (Thallium). Insecticides are discussed in Chaps. 109 and 110. Herbicides are discussed in Chap. 111 and fumigants including methyl bromide, in Chap. 112.

EPIDEMIOLOGY: RODENTICIDES

Rodenticide exposures in the United States are most commonly associated with young children. More than 85% of reported exposures involved children

TABLE 104–1. EPA Toxicity Classifications

Category and Signal Word	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Inhalation LC_{50} (mg/L)	Eye Irritation	Skin Irritation
I Danger	<50	0–199	0–0.049	Corrosive: corneal opacity not reversible within 21 d	Corrosive
II Warning	50–499	200–1999	0.05–0.49	Corneal opacity reversible within 8–21 d; irritation persisting for 7 d	Severe irritation at 72 h
III Caution	500–4999	2000–20,000	0.5–5.0	Corneal opacity; irritation reversible within 7 d	Moderate irritation at 72 h
IV None	>5000	>20,000	>5.0	Irritation cleared within 24 h	Mild or slight irritation at 72 h

younger than 6 years of age. Remarkably, despite the very large number of exposures, no more than five deaths are reported each year from rodenticide poisoning. These deaths typically result from long-acting anticoagulants, strychnine, and zinc phosphide.

THE DEFINITION AND CLASSIFICATION OF RODENTICIDES

Rodenticides are a disparate group of chemicals bearing little or no relationship to one another, apart from their current or historic use as rodenticides. Rodenticides have been classified in several different ways: (a) as inorganic and organic compounds; (b) by animal selectivity; (c) by nature and onset of symptoms; and (d) according to their LD_{50} in rats. Table 104–2 summarizes this last organizing structure.

DANGEROUS OLD, NEW, AND UNUSUAL RODENTICIDES: THE WORLDWIDE PROBLEM

The confusion caused by other types of pesticides inappropriately used as rodenticides is occasionally compounded when a dangerous rodenticide favored in one part of the world is introduced and used in a different area, or when a highly toxic, previously abandoned rodenticide is "rediscovered." All three types of problems have been increasingly reported. Accessibility to the products and global travel may explain part of the problem.

Tetramethylene Disulfotetramine (Tetramine, TETS, TEM)

Several reports have appeared describing the toxicity of the illegal Chinese rodenticide tetramine. Tetramine is unavailable in the United States and was banned in China in 1984. In September 2002, a deliberate adulteration of restaurant food with tetramine by a competing restaurant owner poisoned 300 people and caused 42 deaths, all in schoolchildren. In that same year, the first known cause of tetramine poisoning in the United States resulted in a 15-month-old infant who was playing with the white powder brought back from China by her parents. The child developed status epilepticus that was refractory to lorazepam, phenobarbital, and pyridoxine.

Tetramine is γ-aminobutyric acid (GABA) antagonist, similar in some respects to picrotoxin with an LD_{50} of 0.1–0.3 mg/kg. Tetramine is more lethal than the World Health Organization's (WHO) most toxic registered pesticide, sodium fluoroacetate. As little as 5–10 mg/kg of tetramine may be lethal.

A variety of methods have been used to treat tetramine poisoning in China, including charcoal hemoperfusion and hemodialysis, but none have proven to be uniformly successful and there are no proven antidotes for tetramine. Management includes the standard approach to gastrointestinal decontamination with activated charcoal and convulsive disorders with benzodiazepines, propofol, and neuromuscular blockers with effective airway protection as needed.

α-Chloralose (Glucochloral, Chloralosane)

α-Chloralose is a central nervous system depressant used as a veterinary anesthetic. Its effects in humans include sedation, anesthesia, myoclonic movements, and seizures. Most human exposures are nonfatal and most current reports originate in Europe. Management in these cases is supportive with the use of airway protection and the administration of activated charcoal.

TABLE 104–2. Management of Specific Rodenticide Ingestions

Rodenticide Name	Physical Characteristics	Toxic Mechanism	Estimated Fatal Dose	Signs and Symptoms	Onset	Antidote and/or Treatment*
Highly Toxic Signal Word: DANGER[a] (LD_{50} <50 mg/kg)						
Thallium (Chap. 96)	White, crystalline, odorless, tasteless	Combines with mitochondrial sulfhydryl groups, interfering with oxidative phosphorylation	14 mg/kg	Anorexia, abdominal pain, diarrhea, painful neuropathy, delirium, coma, seizures, alopecia (late), Mees lines	GI symptoms acutely, other symptoms 12–14 h delay	Activated charcoal, Prussian blue
Sodium monofluoroacetate (SMFA, compound 1080)	White, crystalline, odorless, tasteless, water soluble	Fluorocitrate; interferes with Krebs cycle	3–7 mg/kg	Seizures, coma, tachycardia, PVCs, VT, VF, ST-T wave changes, rhabdomyolysis	½–20 h	Experimental regimens: see text
Sodium fluoroacetamide (compound 1081) (Chap. 106)	Same as SMFA	Same as SMFA	13–14 mg/kg	Same as SMFA	Same as SMFA	Same as SMFA
Strychnine (Chap. 108)	Bitter taste	Glycine receptor antagonist on spinal cord motor neurons	Children: 15 mg Adults: 1–2 mg/kg	Restlessness, anxiety, twitching, hyperextension alternating with relaxation, intense pain, trismus or facial grimacing ("risus sardonicus"), inability to swallow, opisthotonos	10–20 min	Quiet room, IV benzodiazepines, neuromuscular blockade
Zinc phosphide (Chap. 112)	Heavy, gray, crystalline powder, water insoluble, "rotten fish" or "phosphorus" odor; normally used as 1% concentration	Releases phosphine on contact with water or acid or in GI tract	40 mg/kg in rats	"Rotten fish" breath odor, black vomitus, GI and cardiovascular toxicity, acute lung injury, agitation, coma, seizures, hepatic/renal toxicity	Within hours; inhalation may have delayed onset	Dilution with water, milk, or $NaHCO_3$

Elemental phosphorus (yellow or white phosphorus) (Chap. 107)	Yellow, waxy paste, fat soluble, water insoluble	Local irritation and burns on contact followed by GI, liver, and renal damage, and interferes with clotting	1 mg/kg (more toxic if dissolved in alcohol, fats, oils)	Skin and GI burns, "smoking" luminescent vomitus and stools with garlic odor, jaundice, dysrhythmias, coma, delirium, seizures, cardiac arrest	1–2 h	Supportive care
Arsenic trioxide (Chap. 85)	White, crystalline powder	Combines with sulfhydryl groups and interferes with a variety of enzymatic reactions	1–4 mg/kg	Dysphagia, nausea and vomiting, bloody diarrhea, cardiovascular collapse, garlic odor, altered mental status, late sensory/motor neuropathy	Symptoms: 1 h Death: 1–24 h	Succimer, dimercaprol until urine arsenic concentration: <50 µg/L Hemodialysis to remove chelation compound if renal failure.
Barium (soluble forms: carbonate, chloride, hydroxide) (Chap. 105)	Yellow, white, slightly lustrous lump	Hypokalemia, neuromuscular blockade	20–30 mg/kg	Headache, paresthesias, peripheral weakness, paralysis, nausea, vomiting, diarrhea, abdominal pain, ECG abnormalities, dysrhythmias, cardiac and pulmonary failure	1–8 h	Orogastric lavage with sodium thiosulfate, potassium replacement
PNU (*N*-3-pyridylmethyl- *N'*-p-nitrophenyl urea, Vacor)	Yellow, resembling cornmeal or yellow-green powder in bait; odor: peanuts	Interferes with nicotinamide metabolism in pancreas (destroying pancreatic beta cells), central and peripheral nervous system, and heart	5 mg/kg	Nausea and vomiting abdominal pain, severe orthostatic hypotension, hyperglycemia with or without ketoacidosis, GI perforations, pneumonia, neuropathy	4–48 h	Nicotinamide (Niacinamide) 500 mg IV or IM, manage diabetic ketoacidosis
Tetramine (tetramethylene disulfotetramine, TETS, TEM)	White powder	Noncompetitive, GABA antagonism by direct blockade of chloride ionophore	5–10 mg/kg	Refractory status epilepticus, fainting, coma, coronary ischemia	1/2–13 h	Benzodiazepines Barbiturates Neuromuscular blockers

(continued)

TABLE 104–2. Management of Specific Rodenticide Ingestions *(continued)*

Rodenticide Name	Physical Characteristics	Toxic Mechanism	Estimated Fatal Dose	Signs and Symptoms	Onset	Antidote and/or Treatment*
Moderately Toxic Signal Word: WARNING[a] (LD_{50}, 50–499 mg/kg)						
α-Naphthylthiourea (ANTU)	Odorless, slightly bitter, fine, blue-gray powder, water-insoluble	Acute lung injury	>4 g/kg	Dyspnea, crackles, clear pulmonary froth, cyanosis, hypothermia	?	Supportive care
Cholecalciferol (vitamin D_3)	0.075% pellets, 364 pellets/oz; (1 pellet = 2308 U vitamin D)	Hypercalcemia	?	Headache, lethargy, weakness, fatigue, renal injury and failure, "metastatic" calcifications due to hypercalcemia	Hours to days	Fluids; if severe: furosemide, prednisone, calcitonin, bisphosphonates
Low Toxicity Signal Word: CAUTION[a] (LD_{50}, 500–4999 mg/kg)						
Red squill (Chap. 114)	Bitter taste	Cardioactive steroid; poisoning	?	Mycocardial irritability, blurred vision, hyperkalemia	30 min–6 h	Digoxin-specific Fab, atropine; see Chap. 62
Norbormide (dicarboximide)	Yellow cornmeal bait, peanut butter, 1% concentration	Vasoconstriction and ischemia in rats only via specific norbormide receptor in rat smooth muscle	?	Transient hypothermia and hypotension with doses up to 300 mg	?	Supportive care
Bromethalin	7.5% concentrate, green pellets, with Bitrex (denatonium benzoate)	Uncouples oxidative phosphorylation; interrupts nerve impulse conduction	?	Muscle tremors, myoclonic jerks, flexion of major muscles, coma?, ataxia, focal motor seizures	Immediate	Supportive care
Anticoagulants: Short Acting (Chap. 57)						
Warfarin	Yellow cornmeal, rolled oats (0.025%)	Anticoagulation via interference with clotting factors II, VII, IX, X; death from hemorrhage	>5–20 mg/d for >5 d	Bleeding with elevated INR	12–48 h	Vitamin K_1, fresh frozen plasma (FFP) as indicated, activated factor VII

Prolin	Warfarin (0.025%) plus sulfaquinoxalin (0.025%)	Anticoagulant antibiotic combination eliminates intestinal vitamin K producing organisms		Bleeding with elevated INR	Delayed several days	Vitamin K_1, fresh frozen plasma (FFP) as indicated, activated factor VII
Anticoagulants: Long Acting						
Hydroxycoumarin						
4-Hydroxycoumarin (brodifacoum, difenacoum)	0.005% grain-based bait	Anticoagulation via interference with clotting factors II, VII, IX, X; death from hemorrhage	?	Bleeding with elevated INR	Delayed several days	Vitamin K_1, fresh frozen plasma (FFP) as indicated, activated factor VII
Warfacide (coumafuryl)	0.5% for dilution to 0.025% white powder, tasteless, odorless			Bleeding with elevated INR	Delayed several days	
Indandiones						
Pindone (Pival)	Moldy, acrid odor, fluffy yellow powder, concentrations 0.005–2.5%	Anticoagulation via interference with clotting factors II, VII, IX, X; death from hemorrhage	?	Chronic ingestion possibly produces cardiac and neurologic symptoms as well as bleeding with elevated INR	Delayed several days	Vitamin K_1, fresh frozen plasma (FFP) as indicated, activated factor VII
Pivalyn	0.5%					
Diphacinone	0.005–2.0%					
Chlorophacinone	0.005–2.5%					
Valone	0.005–2.5%					

[a]The LD_{50} values used in this table are derived from data on acute oral ingestions of the commercial product by rats. In some cases the commercial product contains a very small percentage of active ingredients. The signal words that appear on labels of registered products may differ from the signal word assigned to the acute oral LD_{50} test because the label may also reflect another study (acute dermal or inhalational LD_{50}) requiring a more severe signal word. See Table 104–1 for the Consumer Product Safety Commission definitions and use of signal words as indicators of potential hazard of toxicity. Peacock D, Biologist, Registrations Division Office of Pesticide Programs, EPA, Washington, DC.

*Gastrointestinal decontamination should be provided as appropriate (Chap. 8); only unique or controversial aspects are discussed in this table.

Salmonella-Based Rodenticides

Salmonella enteritides, a human pathogen is an active ingredient in rodenticides still produced and used in Central America and Asia. In 1954, and again in 1967, the World Health Organization recommended against using *Salmonella*-based rodenticides because of their threat to human health.

MANAGING THE PATIENT EXPOSED TO AN UNKNOWN RODENTICIDE

First, as always, assure adequate breathing and circulation. If the patient is initially stable, the next priority is to make every effort to fully identify the type and quantity of rodenticide ingested.

If the rodenticide and its package material are not brought with the patient, someone should be sent to bring them back to the emergency department. If the rodenticide container is labeled, and the information is telephoned back to the emergency department, care should be taken to obtain the *full* name, not just the brand name. The names are frequently used interchangeably by manufacturers.

Immediately following an ingestion and prior to the development of signs and symptoms of toxicity, there is no rodenticide currently in use for which orogastric lavage followed by activated charcoal, and possibly an intestinal evacuant cathartic, is *contraindicated*, although they may be unnecessary. After the patient is symptomatic, however, orogastric lavage, activated charcoal, and catharsis must be individualized according to the specific toxin and the patient's clinical condition.

While awaiting full identification of the rodenticide, a careful physical examination should be performed, searching for toxic signs that indicate a specific rodenticide (Table 104–2). If a toxic syndrome is identified, aggressive management, including the use of specific antidotes, may be necessary.

If every effort to identify the rodenticide fails, the following diagnostic evaluation may be indicated: A complete blood count (CBC) or hemoglobin (Hgb)/hematocrit (Hct) determination and international normalized ratio (INR) (prothrombin time) will help to diagnose and manage repetitive ingestions of the older warfarin-type rodenticide, chronic ingestions of the newer *superwarfarin anticoagulant* rodenticides, and a large, single ingestion of a superwarfarin a few days after ingestion. Following a single acute ingestion, the CBC and INR will not be useful until 48 hours later. Serum glucose, potassium, and bicarbonate determinations will identify hyperglycemia and ketoacidosis caused by *Vacor*, and an elevated serum calcium concentration suggests *cholecalciferol* (*vitamin D_3*) ingestion. Liver enzymes, blood urea nitrogen (BUN), and creatinine are useful baseline determinations for rodenticides that cause renal or hepatic damage (eg, *zinc phosphide*, *yellow phosphorus*, *cholecalciferol*). A serum sample and 50 mL of urine should be obtained and sent to the toxicology laboratory with the request to hold it for possible heavy metals screening, especially if the patient is vomiting. Finally, if indicated by history or symptomatology, additional specimens may be collected for specific rodenticide determinations (eg, *thallium*, *strychnine*). A digoxin concentration might offer a clue to Red Squill ingestion, as might an ECG suggestive of cardioactive steroid poisoning (Chap. 62). Chest and abdominal radiographs may be useful because of the radiopaque nature of some of the uncommonly used rodenticides (Chap. 6).

If patients remain asymptomatic past 4–6 hours of observation, the most likely possibilities are an anticoagulant or a nontoxic ingestion of any other rodenticide. Discharge is possible if the patient is psychiatrically stable and poses no harm to him or herself or to others.

105 Barium

CHEMISTRY

Elemental barium is not found in nature; it normally occurs as an oxide, dioxide, sulphate (barite), or carbonate (witherite). Chemically, barium resembles calcium more than any other element. Barium salts may be either water soluble or insoluble. The soluble salts—acetate, chloride, hydroxide, oxide, nitrate, and (poly)sulfide—are the ones most commonly associated with toxicity. Barium (poly)sulfide may also produce toxicity through the formation of hydrogen sulfide when it combines with the acid normally present in the stomach. The solubility of barium carbonate is low at a normal pH, but increases significantly when the pH is lowered. In gastric acid, conversion to the highly soluble barium chloride occurs. Insoluble salts, such as arsenate, carbonate, chromate, fluoride, oxalate, and sulfate, are rarely associated with toxicity (Table 105–1).

HISTORY AND EPIDEMIOLOGY

Barium poisoning is rare, with less than 100 exposures reported annually to the Toxic Exposure Surveillance System (TESS) database. Toxicity is most commonly reported following the intentional ingestion of soluble salts found in rodenticides, insecticides, or depilatories. Despite barium sulfate being insoluble, rare cases of unintentional toxicity have been reported during radiographic procedures, including complications associated with oral and rectal administration. Toxicity and death occurred when soluble barium salts unintentionally contaminated contrast solution and flour.

TOXICOKINETICS

Toxicity can occur from ingestion of as little as 200 mg of barium salt, although oral lethal doses are reported to range from 1–30 g barium salt. Following ingestion, 5–10% of soluble barium salts are absorbed, with the rate of absorption dependent on the water solubility of the salt. The time to peak serum concentrations is 2 hours. Plasma barium concentrations fall with a half-life between 18 hours and 3.6 days. Renal elimination accounts for 10–28% of excretion. Death from an ingestion with barium chloride was associated with the following barium concentrations at autopsy: blood, 9.9 mg/L; bile, 8.8 mg/L; urine, 6.3 mg/L; and gastric contents, 10 gm/L.

CLINICAL EFFECTS

Abdominal pain, nausea, vomiting, and diarrhea commonly occur within 1 hour of ingestion. Esophageal injury and hemorrhagic gastritis are also reported. Severe hypokalemia is the cardinal feature of barium toxicity and can occur within 2 hours following oral or parenteral exposure.

Barium induces hypokalemia by two synergistic mechanisms: competitive blockade of the potassium rectifier channel, which is responsible for the efflux of intracellular potassium out of the cell, and a direct increase in cell

TABLE 105–1. Available Barium Salts

Barium Salt	Solubility*	Common Uses
Acetate	58.8	Textile dyes
Carbonate	0.02 Solubility increases markedly in an acid pH. Also conversion to barium chloride	Rodenticide, welding fluxes, pigments, glass, ceramics, pyrotechnics, electronic devices, welding rods, ferrite magnet materials, optical glass, manufacture of caustic soda and other barium salts
Chloride	375 (26°C)	Textile dyes, barium salts, pigments, boiler detergents, in purifying sugar, as mordant in dyeing and printing textiles, as water softener, in manufacture of caustic soda and chlorine, polymers, stabilizers
Fluoride	1.2 (25°C)	Welding fluxes
Nitrate	87	Optical glass, ceramic glazes, pyrotechnics (green light), fireworks, explosives, antiseptic preparation
Oxide	34.8	In glass, ceramics, refining oils and sugar, as an additive in petroleum products and also as materials of plastics, pharmaceuticals, polymers, glass and enamel industries.
Styphenate	?	Propellent used in manufacture of explosive detonators
Sulfate	0.002	Radiopaque contrast media, manufacture of white pigments, paper making
Sulfide	0.9	Depilatories, manufacture of fluorescent tubes

*In g/L at 68°F (20°C); where the solubility was not measured at 68°F (20°C), the temperature (°C) used is shown in parentheses.

membrane permeability to sodium, which causes an increase in Na^+-K^+ pump electrogenesis, leading to a shift of extracellular potassium into the cell.

Intracellular trapping of potassium leads to depolarization and paralysis. There may also be a direct effect of barium on either skeletal muscle or neuromuscular transmission. Additionally, the inhibition of potassium channels increases vascular resistance and reduces blood flow and is the likely mechanism for hypertension and lactic acidosis.

DIAGNOSTIC STUDIES

Serum barium concentrations are not readily available, but values greater than 0.2 mg/L are considered abnormal. Following acute exposures, patients should have serum electrolytes (particularly potassium and phosphate) measured hourly while performing continuous ECG monitoring. Acid–base status, renal function, and creatine phosphokinase (CPK) should also be measured. A plain abdominal radiograph might demonstrate the presence of barium, but the sensitivity and specificity of radiography has never been determined.

MANAGEMENT

Patients should be admitted to a monitored bed with the facilities for respiratory support readily available. Patients who are asymptomatic at 6 hours with normal potassium concentrations can be discharged.

Decontamination

Activated charcoal is unlikely to be effective. Orogastric lavage should be considered in patients who present early after ingestion, but is unlikely to provide extra benefit in patients who are already symptomatic or those who have had spontaneous emesis. Oral sodium sulfate administration may prevent absorption by precipitating unabsorbed barium ions to insoluble, nontoxic barium sulfate. Oral magnesium sulfate has also been used with success. The oral dose of magnesium sulfate is 250 mg/kg for children and 30 g for adults. Because intravenous magnesium sulfate or sodium sulfate may lead to renal failure as a result of precipitation of barium in the renal tubules, it is not recommended.

Patients in respiratory failure should receive assisted ventilation. Aggressive correction of hypokalemia is important to minimize the risk or to treat cardiac dysrhythmias. Large doses of potassium (400 mEq in 24 hours) may be required to correct serum potassium, but may still not improve muscle strength. As hypokalemia is caused by intracellular sequestration of potassium, potassium supplementation increases the total body potassium load. In this situation, rebound hyperkalemia may occur when barium is eliminated, especially when a patient has impaired renal function.

ELIMINATION ENHANCEMENT

Hemodialysis has been reported to improve severe barium toxicity. Additionally, in a case report, continuous venovenous hemodiafiltration (CVVHDF) tripled the measured barium elimination, reduced serum barium half-life by a factor of three, stabilized serum potassium concentrations, and rapidly improved motor strength, with complete neurologic recovery within 24 hours. Either method of enhanced elimination should be considered in any severely symptomatic patient who does not respond to correction of hypokalemia.

106 Sodium Monofluoroacetate and Fluoroacetamide

HISTORY AND EPIDEMIOLOGY

Sodium monofluoroacetate (SMFA) is synthesized by plants such as gifblaar (*Dichapetalum cymosum*), native to Brazil, Australia, and South and West Africa. The compound (also known as 1080) was developed as a rodenticide. Fluoroacetamide, a similar compound, is known as Compound 1081. Use of either was banned in the United States in 1972 except in the form of collars intended to protect sheep and cattle from coyotes. Currently, SMFA is used extensively in New Zealand and Australia.

PHARMACOKINETICS AND TOXICODYNAMICS

Sodium monofluoroacetate is an odorless and tasteless white powder with the consistency of flour. SMFA and fluoroacetamide are well absorbed orally, and poisoning has also occurred from inhalation. Detailed toxicokinetic data are lacking in humans. The plasma half-life is estimated to be 6.6–13.3 hours in sheep and the estimated LD_{50} (median lethal dose for 50% of test subjects) in humans is 2–5 mg/kg.

PATHOPHYSIOLOGY

Sodium monofluoroacetate is an irreversible inhibitor of the tricarboxylic acid cycle within the mitochondria. Monofluoroacetic acid enters the mitochondria where it is converted to monofluoroacetyl-coenzyme A (CoA) by acetate thiokinase. Then citrate synthase joins the monofluoroacetyl-CoA complex with oxaloacetate to form fluorocitrate. Finally, fluorocitrate covalently binds aconitase, preventing the enzyme from any further interaction in the tricarboxylic acid cycle (see the Krebs cycle table in biochemistry, Fig. 13–1).

Inhibition of aconitase impairs energy production, leading to metabolic acidosis with an elevated lactate concentration. In addition, the increase in citrate, which chelates divalent cations, causes hypocalcemia. Other tricarboxylic acid cycle intermediates may also contribute to the toxicity.

CLINICAL MANIFESTATIONS

Most patients will develop symptoms within 3–6 hours from the time of exposure. The most common symptoms of exposure recorded at the time of emergency department presentation were nausea and vomiting (74%), diarrhea (29%), agitation (29%), and abdominal pain (26%). Death typically occurs within 72 hours of admission to the hospital. Respiratory distress, hypotension, and/or seizures are prognostic of death.

DIAGNOSTIC TESTING

Although SMFA and fluoroacetamide can be confirmed with gas chromatography-mass spectrometry and thin-layer chromatography, neither of these studies can be performed in a clinically relevant time period. A combination of history, signs, symptoms, and common laboratory tests can assist with the

diagnosis. A complete blood cell count may reveal leukocytosis, and electrolytes may demonstrate hypokalemia, hypocalcemia, and an acidosis.

The ECG findings will be consistent with the electrolyte abnormalities; a prolonged QTc, atrial fibrillation with a rapid ventricular response, ventricular tachycardia, and other dysrhythmias are all described.

TREATMENT

Initial decontamination should include removal of clothes and cleansing of skin with soap and water. Since there is no antidote for SMFA or fluoroacetamide poisoning, orogastric lavage should be considered for exposed patients who present to the emergency department prior to significant emesis. All patients should receive activated charcoal. Animal data suggest that colestipol may be effective and should be considered in life-threatening cases.

In animal models, the molecules ethanol and glycerol monoacetate (monoacetin) are thought to be antidotes acting as acetate donors for ultimate incorporation into the tricarboxylic acid cycle. Both of the molecules are converted to acetyl-CoA and compete for binding of citrate synthase with monofluoroacetyl-CoA. Ethanol has been used in human cases, although the appropriate dose is unknown. A reasonable therapeutic dose that is considered safe is to achieve an ethanol serum concentration of 100 mg/dL, which is similar to the recommendation for ethylene glycol or methanol poisoning. In a mouse model, a therapeutic combination of calcium salts, sodium succinate, and α-ketoglutarate resulted in improved survival. The rationale of using these antidotes is to provide tricarboxylic acid cycle intermediates that are distal to the toxin's inhibition of aconitase in an attempt to improve energy production.

Hypotension and shock should be treated with intravenous fluids followed by a vasopressor such as norepinephrine. Supportive care, correction of electrolyte abnormalities (calcium and potassium), ethanol infusion, and monitoring for dysrhythmias and seizures are indicated.

107 Phosphorus

HISTORY AND EPIDEMIOLOGY

The word *phosphorus* comes from the ancient Greek *phos*, which means light, and *phorus*, which means bringing. White phosphorus gained public notoriety as the main ingredient in strike-anywhere matches. Workplace exposure to phosphorus-produced "phossy jaw," or mandibular necrosis, was first documented in 1838. Accounts of patients suffering from phossy jaw describe loss of teeth, softening or destruction of the mandible, and formation of abscesses discharging foul-smelling pus. Because of the fire hazard presented by strike-anywhere matches, their use was discontinued. Today, matches use red phosphorus in the striking pad on the matchbook. Today, white phosphorus is used commercially to manufacture insecticides and fertilizer, as an incendiary, and in fireworks.

CHEMISTRY

Elemental phosphorus exists in three allotropes: black phosphorus, a nontoxic compound that does not ignite spontaneously; red phosphorus, a fairly innocuous phosphorus intermediate in reactivity between black and white phosphorus; and white phosphorus, a highly reactive and dangerous element. White phosphorus is a tetramer, P_4, which is a waxy paste, insoluble in water. The presence of impurities in white phosphorus accounts for the general description of white phosphorus as yellow phosphorus. White phosphorus undergoes rapid oxidation upon contact with oxygen, with the resultant liberation of heat, light, and dense white smoke. Phosphorus pentoxide generates phosphoric acid when dissolved in water. Following the explosion white phosphorus is broadly disseminated, in a dense cloud of white smoke with a garlic odor. The smoke is phosphoric acid, which can produce pulmonary, ophthalmic, and dermal irritation.

Red phosphorus differs from the white allotrope by its crystalline form, its lack of phosphorescence, and its markedly reduced reactivity with oxygen. Red phosphorus will slowly degrade to highly toxic phosphine gas (PH_3) and phosphorous acid. Black phosphorus is produced by heating white phosphorus with a mercury catalyst, forming a graphite-like sheet of phosphorus atoms. Black phosphorus is the least reactive, does not readily ignite, and has little commercial value.

Because the majority of toxicity reported from elemental phosphorus is caused by the white allotrope, phosphorus in this chapter refers to the white allotrope, unless otherwise specified.

TOXICOKINETICS

White phosphorus is rapidly absorbed from the intestinal tract and subsequently taken up primarily by the tissues of the liver, renal cortex, bowel mucosa, epidermis, hair follicles, pancreas, and adrenal cortex. Within several hours of ingestion 69–73% of the total ingested dose is identified concentrated in the liver. Because phosphorus is highly lipid soluble, significant absorption can also occur after skin or mucosal exposure. Penetrating wounds

and dermal burns enhance the systemic absorption of phosphorus. The lethal dose is suggested to be 1 mg/kg.

PATHOPHYSIOLOGY

Hepatic

Phosphorus increases oxygen consumption in the hepatocyte. Uncoupling of oxidative phosphorylation is the likely mechanism, and there is a decrease in intrahepatocyte adenosine triphosphate (ATP) levels. Massive hepatic steatosis is a hallmark of white phosphorus toxicity, with a rise in hepatic triglycerides beginning within 2 hours and peaking in 36 hours. Hepatic necrosis may be prominent, particularly in zone 1, in distinction to most other classic hepatotoxins, such as acetaminophen, which produce zone 3 necrosis.

Skin, Mucous Membranes, and Gastrointestinal Tract

Phosphorus can cause both thermal and chemical injury. The gastrointestinal tract may be relatively spared compared to equivalent exposure of the skin, likely because of the low concentration of oxygen in the gastrointestinal tract. The mucous membranes may similarly be affected by white phosphorus, much of it mediated by phosphoric acid.

Cardiovascular

The likely mechanism of phosphorus-induced dysrhythmias is profound electrolyte abnormalities, including hypocalcemia and hyperkalemia.

Nervous System

Nervous system manifestations of white phosphorus poisoning appear to be more related to the development of hypocalcemia than to direct toxic effect on the tissues.

Electrolyte Homeostasis

Hyperphosphatemia is a direct result of absorption and conversion to phosphoric acid excess and subsequent deproteination. Calcium complexes with phosphate, causing hypocalcemia, and may precipitate within tissues in forms such as hydroxyapatite. Hyperkalemia may result from the profound hypocalcemia (as in hydrofluoric acid poisoning) or it can occur as a result of renal failure.

CLINICAL MANIFESTATIONS

Overall mortality ranges from 20–50%. Poor prognostic indicators include ingestion of greater than 1 mg/kg; signs of severe electrolyte disturbance, such as reversal of Ca^{2+}:PO_4^{3-} ratio, mental status changes, prolongation of QTc, and ST segment and T-wave abnormalities; 10-fold or greater increase in alanine aminotransferase (ALT); coagulopathy; and peak liver enzymes reached within 36 hours of ingestion.

Three stages are typically described. The first, which lasts for hours to days, is marked by irritation and injury of the gastrointestinal tract. In the second stage, the gastrointestinal symptoms may resolve. This period can last for several days. In the third stage, patients develop cardiac, hepatic, or renal tox-

icity. Recovery, if it occurs, takes place over days to weeks. However, a review of 41 fatal, reported cases of white phosphorus ingestion suggests a clinical course that differs from this description. More than half the deaths occurred in the first day, and the cause of death, when known, was cardiac in nature, presumably dysrhythmic because of electrolyte abnormalities. Deaths as a result of fulminant hepatic failure occur within the first week.

White phosphorus produces hepatotoxicity in a predictable and dose-dependent manner. Abnormal aminotransferases occur in approximately half of phosphorus-poisoned patients, and usually begin to rise within 24 hours of exposure.

Phosphorus skin burns are very painful, with a necrotic appearance, yellowish color, and garlic odor. Human experience and animal models suggest a second- or third-degree burn of 10–15% body surface area may result in death from phosphorus absorption.

Mucosal surfaces that are directly affected by phosphorus suffer the same chemical burns noted on the skin. Following exposure to phosphorus smoke, membranes in exposed areas such as the mouth, nose, and eyes may develop swelling, injection, and other signs of irritation. Oropharyngeal burns, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal hemorrhage may occur following ingestion. Hematemesis occurs in approximately 30% of patients who ingest phosphorus and postmortem examinations of the intestines show diffuse hemorrhages. The vomitus and stool are typically described as having a garlic odor. Case reports describe that the effluent emits smoke—a "smoking stool"—and is phosphorescent.

Early death following white phosphorus exposure is commonly a result of cardiovascular collapse. In one case, this was caused by decreases in cardiac contractility and systemic vascular resistance. Electrocardiographs performed during the first 12 hours show abnormalities, including bradycardia, atrial fibrillation, QTc prolongation, ST segment depression, T wave changes, bradycardia, and low-voltage QRS complexes, in 70% of the patients. These manifestations likely reflect electrolyte abnormalities.

Central nervous system (CNS) signs, which include irritability, anxiety, agitation, confusion, lethargy, delirium, hallucinations, seizures, and coma, are often the first manifestations of toxicity. Patients who develop CNS signs or symptoms before other organ systems are affected have a mortality rate of 73%. In the peripheral nervous system, hypocalcemia manifests as paresthesias, carpopedal spasm, tetany, and even laryngeal stridor or opisthotonus.

Renal failure and hyperkalemia are not prominent findings in phosphorus poisoning, but are noted in some cases. Two hypotheses for renal failure are a direct toxic effect of white phosphorus on the kidney, and acute tubular necrosis because of shock.

ASSESSMENT AND MANAGEMENT

Protection of Healthcare Personnel

Care must be taken to prevent exposure of healthcare personnel. Phosphorus contained in vomitus or stool can be hazardous. Personnel should wear protective equipment to prevent direct contact with phosphorus.

Supportive and Standard Care

Life-support measures, such as airway protection and fluid resuscitation, should be provided. A complete blood count, hepatic enzymes, coagulation

parameters, basic metabolic panel, serum phosphate, and serum calcium should be measured. Electrolytes, in particular, should be assayed frequently. Hypocalcemia, hyperphosphatemia, and hyperkalemia should be expeditiously treated using standard modalities. Frequent measurement of vital signs and continuous cardiac monitoring are essential. Renal function, as well as urine output, must be evaluated. Ophthalmic irrigation should be performed if eye irritation is present.

Skin Decontamination

The patient with a cutaneous exposure should be immediately washed with or immersed in water. Irrigation is the only treatment shown to decrease burn size, length of hospital stay, and mortality. Any areas where white phosphorus may remain must be kept wet at all times, as the substance may reignite if it is exposed to ambient oxygen. Copper sulfate solutions are occasionally recommended for conversion of particulate phosphorus to the less harmful copper phosphate, which is black, making débridement easier. However, copper sulfate can inhibit glucose-6-phosphate dehydrogenase, leading to lethal hemolysis, raising a significant concern about its potential benefit. Remaining particulate phosphorus may be identified using a Woods lamp, as phosphorus fluoresces easily. A thorough débridement must be performed as any remaining phosphorus can be systemically toxic.

Gastrointestinal Decontamination

Early lavage of the stomach has been recommended, without supporting data, given the high mortality associated with ingestion and the lack of effective antidotes. Although there are no data evaluating the ability of activated charcoal to adsorb phosphorus, no effective antidote exists, and esophageal burns are not prominent. Consequently, the administration of oral activated charcoal is appropriate for patients who have ingested phosphorus.

Whole-bowel irrigation with polyethylene glycol may decrease the absorption of phosphorus by mixing the toxin in a nonabsorbable carrier and removing it from the GI tract. Given the highly toxic nature of phosphorus, this treatment should be attempted for consequential ingestions.

Instillation of 1:5000 potassium permanganate solution into the stomach theoretically will convert ingested white phosphorus to a less harmful oxide. This treatment has been used on many patients, but no trial has been done to demonstrate a benefit. This therapy is not readily available, is high risk from a chemical perspective, is without any sound clinical basis, and is not indicated.

Other Antidotal Therapies

Since *N*-acetylcysteine (NAC) may protect against liver injury, it should be given in standard dosing if not contraindicated. A prospective human study reached the conclusion that corticosteroids are not helpful in reducing the hepatotoxic effects of white phosphorus. In small animal studies, ubiquinone, cysteine, and sulfate treatments were shown to prevent liver damage to some degree. No human data exist on these therapies.

108 Strychnine

Strychnine is found naturally in *Strychnos nux vomica*, a tree native to tropical Asia and North Australia, as well as in *Strychnos ignatii* and *Strychnos tiente*, trees that are native to South Asia. The alkaloid is an odorless, colorless, crystalline powder, which has a bitter taste when dissolved in water.

Strychnine was first introduced as a rodenticide in 1540. It was subsequently used medically as a cardiac, respiratory, and digestive stimulant, an analeptic, and an antidote for barbiturate and opioid overdoses. In 1982, 172 commercial products contained strychnine, including 77 rodenticides, 25 veterinary products, and 41 products for human use. Currently, strychnine is restricted to nonhuman use and is mainly used as an insecticide, pesticide, and rodenticide. Most products contain about 0.25–0.35% strychnine.

EPIDEMIOLOGY

Strychnine poisoning caused significant mortality in the past, especially in children. In the 1920s, strychnine killed more than three Americans every week. In 1932, it was the most common cause of lethal poisoning in children and one-third of the unintentional poison deaths of children younger than 5 years old were attributed to strychnine. Currently, although strychnine poisoning is uncommon in United States, deaths are still reported. Exposures result from suicidal and homicidal attempts, unintentional poisoning from a Chinese herbal medicine (Maqianzi), a Cambodian traditional remedy (slang nut), and adulteration of street drugs.

TOXICOKINETICS

While the lethal dose of strychnine is commonly quoted at 50–100 mg (1–2 mg/kg), deaths from doses as low as 5–10 mg are reported. Some of this variation can be attributed to the route of administration, with parenteral being more toxic than oral.

Strychnine is rapidly absorbed from the gastrointestinal tract, mucous membranes, and the parenteral route. There is also one case report of poisoning via dermal absorption. There is minimal protein binding and a large volume of distribution (13 L/kg). The highest concentrations of strychnine are found in the liver, bile, blood, and gastric contents.

Strychnine is metabolized by hepatic cytochrome P450 microsomes, which produce strychnine *N*-oxide as the major metabolite. Several urinary metabolites are identified and 1–30% of strychnine is excreted unchanged in urine, with a decreasing proportion when larger amounts are ingested. In humans, elimination follows first-order kinetics with a half-life of 10–16 hours.

Pathophysiology

Strychnine is a postsynaptic, competitive, glycine-receptor antagonist. With the loss of the glycine inhibition to the motor neurons in the ventral horn, there is an increased impulse transmission to the muscles, resulting in generalized muscular contraction. For comparison, tetanus toxin causes similar muscular contractions by preventing the release of glycine from the presyn-

aptic neuron. In dogs, strychnine has positive chronotropic and inotropic effects on the heart, but this effect is unlikely to exert major consequences in human poisoning.

Clinical Manifestations

Symptoms begin about 15–60 minutes following oral ingestion, and although less-well documented, are expected to be even faster with parenteral or nasal administration. Delayed presentations are rarely reported, with a 10-hour delay to symptoms in one case. Typical symptoms are involuntary generalized muscular contractions resulting in neck, back, and limb pain. The contractions are easily triggered by trivial stimuli and usually last for 30 seconds to 2 minutes in each episode, repeatedly for a duration of 12–24 hours. These unopposed contractions result in the classical signs of opisthotonus, facial trismus, and risus sardonicus, with flexion of the upper limbs and extension of lower limbs. Hyperreflexia, clonus, and nystagmus are also noted. Because strychnine affects glycine inhibition mainly in the spinal cord, the patient retains a normal level of consciousness until metabolic complications are severe. These characteristics often result in descriptions such as "conscious seizure" or "spinal seizure" being used to describe strychnine poisoning.

Hypotension and hypertension, as well as bradycardia and tachycardia, are all reported. Hyperthermia results from the increased muscular activity, and severe hyperthermia is reported. Other nonspecific signs and symptoms include dizziness, vomiting, and chest and abdominal pain.

Death results mainly from hypoxia and hypoventilation secondary to muscle contractions. Later life-threatening complications include rhabdomyolysis with subsequent myoglobinuria and acute renal failure, hyperthermia with multiorgan failure, pancreatitis, aspiration pneumonia, anoxic brain injury, and adult respiratory distress syndrome. Rarely, local neuromuscular sequelae such as weakness, myalgias and compartment syndrome are reported.

Differential Diagnosis

The diagnosis of strychnine poisoning is mainly established on clinical grounds, although several etiologies need to be considered. Tetanus will have similar muscular hyperactivity as tetanospasmin inhibits the release of glycine in the spinal cord. However, tetanus is expected to have a less rapid onset and a more protracted course. Generalized seizures can be differentiated by the normal sensorium, at least in the initial phase of the clinical course, and by an electroencephalogram (EEG) if necessary. Absence of focal neurologic deficits and a computed tomography (CT) scan help to exclude a structural brain lesion, and a lumbar puncture is helpful to exclude meningitis or encephalitis. Hypocalcemia, hyperventilation, and myoclonus secondary to renal or hepatic failure are evaluated by relevant routine laboratory testings. Although a drug-induced dystonic reaction should be considered when there is relevant drug history, dystonic reactions are usually static, and strychnine poisoning results in dynamic muscular events.

Diagnostic Testing

Most laboratory abnormalities associated with strychnine poisoning are a result of the intense muscle contractions. Metabolic acidosis correlates with serum lactate and respiratory acidosis results from hypoventilation from diaphragmatic

and respiratory muscle failure. Survival in patients with serum pHs in the range of 6.5–6.6 is common. Other laboratory abnormalities may demonstrate rhabdomyolysis, hyperkalemia, acute renal insufficiency, a stress-induced leukocytosis, elevated liver enzymes, hypocalcemia, hypernatremia, and hypokalemia.

Strychnine can be detected by various methods such as thin-layer chromatography, high-performance liquid chromatography, ultraviolet spectrometry, a simple colorimetric reaction, gas chromatography–mass spectrometry, gas chromatography–flame ionization detector, and capillary electrophoresis. With the exception of the bedside colorimetric reaction, none of these tests are routinely available in a timeframe to assist in clinical decisions.

Management

Induced vomiting by syrup of ipecac is absolutely contraindicated because of the risk of aspiration and potential loss of airway control as a result of the expected rapid onset of muscle contractions in strychnine poisoning. Orogastric lavage should be considered in terms of potential benefits and risks. It is important to protect and secure the airway with an endotracheal tube before attempting to perform gastric lavage when it is indicated. Activated charcoal binds strychnine effectively, and should be given at a dose of 1 g/kg body weight. Forced diuresis, peritoneal dialysis, hemodialysis, and hemoperfusion are not indicated.

Supportive treatment remains the most important aspect of care, and the objective is to stop the muscle hyperactivity as soon as possible. At all times, unnecessary stimuli and manipulation of the patient should be avoided as these trigger muscle contractions. Benzodiazepines remain the first-line treatment. The initial dose of benzodiazepine should be the standard dose used for agitation and hyperactivity, although doses greater than 1 mg/kg diazepam or its equivalent may be needed. Dosing should be repeated at appropriate intervals until the patient becomes relaxed. Barbiturates or neuromuscular blockade may be required if benzodiazepines do not produce rapid control. It is important to remember that strychnine has no direct effects on consciousness, so that sedation must always accompany neuromuscular blockade. Generally therapy is continued for about 24 hours and then the patient can be weaned from the respirator as tolerated.

Hyperthermia should be treated aggressively by active cooling with ice water immersion or mist and fan. Metabolic acidosis rapidly subsides when muscular activity is controlled. Treatment for rhabdomyolysis includes adequate fluid administration to ensure good urine output (>1 mL/kg/h), and alkalinization to prevent myoglobin precipitation in renal tubules. The management in the first few hours of strychnine poisoning is crucial for survival.

For those patients unintentionally exposed to strychnine who remain without symptoms, an observation period of 12 hours is sufficient to exclude a significant risk.

109 Insecticides: Organic Phosphorus Compounds and Carbamates

EPIDEMIOLOGY

The first potent synthetic organic phosphorus anticholinesterase was synthesized in 1854. Today, the World Health Organization estimates that at least 1 million unintentional poisonings and 2 million suicide attempts occur annually from these agents. However, these figures likely neglect numerous unreported and possibly unrecognized illnesses resulting from environmental exposure. Although most cases come from developing nations, cases also occur frequently in the United States.

PHARMACOLOGY

Organic Phosphorus Compounds

Organic phosphorus compounds are extremely well absorbed from the lungs, gastrointestinal tract, skin, mucous membranes, and conjunctiva following inhalation, ingestion, or topical contact. The presence of broken skin, dermatitis, and higher environmental temperatures enhance cutaneous absorption. Most organic phosphorus compounds are lipophilic. Radiolabeled parathion injected into mice distributes most rapidly into the cervical brown fat and salivary glands, with high concentrations also measured in the liver, kidneys, and ordinary adipose tissue. Since adipose tissue gradually accumulates the highest concentrations and serves as a reservoir, toxicity may recur in patients when fat stores of unmetabolized organic phosphorus compounds are mobilized.

Peak concentrations of organic phosphorus compounds are measured 6 hours after ingestion in humans. Although serum half-lives of these compounds range from minutes to hours, prolonged absorption or redistribution from fat stores may allow for measurement of circulating concentrations for up to 48 days.

Organic phosphorus compounds are thought to be metabolized by various mixed function oxidases in the liver and intestinal mucosa, but the exact pathways are not yet well understood. The phosphorylating ability of these substances is lost when any of the side chains are hydrolyzed. Inactive metabolites of these compounds are excreted in the urine. "Direct"-acting organic phosphorus compounds inhibit acetylcholinesterase (AChE) without being structurally altered by the body. Prodrugs, such as parathion and malathion, require metabolism to become active.

Carbamates

Carbamate insecticides are well absorbed across skin and mucous membranes, as well as by inhalation and ingestion. Peak serum concentrations of some compounds are measured 30–40 minutes following ingestion. Most carbamates undergo hydrolysis, hydroxylation, and conjugation in the liver and intestinal wall, with 90% excreted in the urine within 3 days. There are two main pharmacokinetic characteristics that distinguish carbamates from organic phosphorus compounds. First, carbamate insecticides do not easily cross into the central nervous system

(CNS). Thus CNS effects of carbamates are limited, although CNS dysfunction may still occur in massive poisonings or may result from hypoxia secondary to pulmonary toxicity and paralysis. Second, the carbamate-cholinesterase bond does not "age" as in organic phosphorus compound poisoning; thus it is reversible, with spontaneous hydrolysis occurring typically within several hours (see below).

PATHOPHYSIOLOGY

Acetylcholine is a neurotransmitter found at both parasympathetic and sympathetic ganglia, skeletal neuromuscular junctions, terminal junctions of all postganglionic parasympathetic nerves, postganglionic sympathetic fibers to most sweat glands, and at some nerve endings within the central nervous system (Fig. 109–1). As the axon terminal is depolarized, vesicles containing acetylcholine (ACh) fuse with the external membrane and rupture, releasing ACh into the synapse or neuromuscular junction. Acetylcholine then binds postsynaptic receptors leading to activation.

Acetylcholinesterase hydrolyzes ACh into two inert fragments: acetic acid and choline. Under normal circumstances, virtually all ACh released by the axon is hydrolyzed almost immediately. Organic phosphorus compounds and carbamates inhibit multiple carboxylic ester hydrolases, including AChE and butyrylcholinesterase (which is sometimes known as either plasma cholinesterase or pseudocholinesterase). This inhibition results from binding to the enzyme, much like normal substrate. Although the splitting of the choline-enzyme bond in normal ACh metabolism is completed within microseconds, the organic phosphorus compound–enzyme bond can persist for many hours. Over time, if not released, a conformational change occurs with a second group leaving, and the organic phosphorus–acetylcholinesterase bond becomes permanent. This process is known as aging. Carbamates differ in that their bond to acetylcholinesterase hydrolyzes spontaneously and does not age.

The net result of enzyme inhibition is an excess of acetylcholine at all cholinergic synapses. This serves as the basis for toxicity.

CLINICAL MANIFESTATIONS

Acute Toxicity (Organic Phosphorous Compounds and Carbamates)

The onset of symptoms varies according to the agent, the route, and the degree of exposure. Patients have become symptomatic as quickly as 5 minutes following massive ingestion, and deaths have occurred within 15 minutes. Most victims of acute poisonings become symptomatic within 8 hours of exposure, and nearly all are symptomatic within 24 hours. The longest delays may occur with agents requiring metabolic activation, such as malathion.

Excessive muscarinic activity can be characterized by several mnemonics, including "SLUD" (salivation, lacrimation, urination, defecation) and "DUMBBELS" (defecation, urination, miosis, bronchospasm or bronchorrhea, emesis, lacrimation, salivation). Of these muscarinic findings, miosis may be the most consistently encountered sign. Bronchorrhea is the most significant muscarinic toxicity and can be so profuse that it mimics pulmonary edema. Excessive stimulation of ganglionic adrenergic neurons produces tachycardia, mydriasis, as well as hyperglycemia, ketosis and leukocyte demargination, resulting in leukocytosis. A prolonged QTc and polymorphous ventricular tachycardia (torsades de pointes) can also occur. Stimulation of sweat glands produces diaphoresis. Excessive stimulation at the neuromuscular junction mimics depolarizing neuromuscular

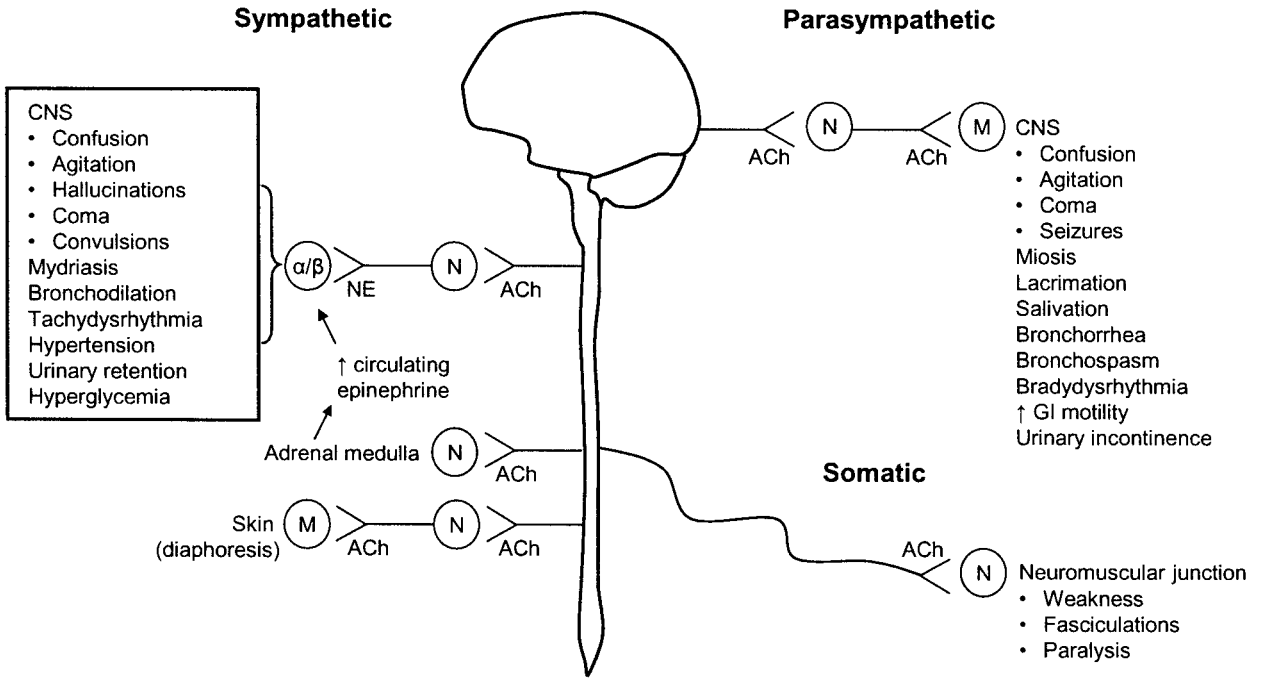

FIG. 109–1. Pathophysiology of cholinergic syndrome as it affects the autonomic and somatic nervous systems. N = nicotinic, M = muscarinic.

blockade (similar to succinylcholine), with fasciculations or weakness followed rapidly by paralysis.

Symptoms may last for variable lengths of time, again based on the agent and the circumstances of the exposure. For example, the more lipophilic compounds, such as dichlofenthion, can cause cholinergic effects for several days following oral ingestion.

Chronic Toxicity (Organic Phosphorus Compounds Only)

Chronic exposure is common in workers who come in contact with small amounts of toxin. Ultimately, cholinesterase inhibition becomes sufficient to produce manifestations identical to those noted with acute poisoning. Because carbamate exposure is rapidly reversible, chronic exposure is unlikely to produce significant toxicity.

Delayed Toxic Syndromes (Organic Phosphorous Compounds Only)

Intermediate Syndrome

Delayed muscle weakness without fasciculations or cholinergic features can occur in patients 24–96 hours after acute organic phosphorus compound poisoning. Most cases of intermediate syndrome develop in patients who present initially with classic cholinergic signs and symptoms and improve over 1–2 days with therapy. Sudden relapse with weakness of the proximal limbs, neck flexors, and muscles of respiration and cranial nerve palsies distinguish this syndrome from classic poisoning.

Although the exact etiology is unknown, popular theories suggest that undertreatment or a redistribution of the lipophilic pesticide from adipose tissue is responsible. With standard treatment (see below) the weakness and paralysis commonly resolve in 5–18 days.

Peripheral Neuropathies

Peripheral neuropathies can occur several days or weeks after single acute exposures and with chronic organic phosphorus pesticide exposures. This disorder results from inhibition of an enzyme named neurotoxic esterase or neuropathy target esterase (NTE). Pathologic findings demonstrate effects primarily on large distal neurons, with axonal degeneration preceding demyelination. Vague distal muscle weakness and pain are often the presenting symptoms, but weakness may progress to paralysis. It is unclear if the onset and clinical course is altered by atropine or pralidoxime. In fact, cholinergic toxicity is not a prerequisite finding. Recovery in these patients is variable over months to years, with residual deficits common.

DIAGNOSTIC TESTING

Although confirmatory testing is not necessary to initiate therapy, it can be valuable in unclear cases, and for decisions about continued care. The presence of insecticides and active metabolites can be confirmed in biologic tissues such as urine, but these tests are only available experimentally. Most commercial laboratories can quantify both butyrylcholinesterase and erythrocyte AChE activity, the latter of which is more reflective of neuronal cholinesterase activity. Once poisoned with an organic phosphorus compound, butyrylcholinesterase remains depressed until new enzyme is synthesized. If erythrocyte AChE activity is not regenerated by oximes (such as prali-

doxime), it remains depressed until red cell turnover occurs. Because the carbamate-cholinesterase bonds spontaneously hydrolyze, red cell cholinesterase activity rapidly returns to normal both in vitro and in vivo following carbamate poisoning.

It is essential to obtain blood samples for cholinesterase activity in the appropriate blood tubes as some tubes contain fluoride, which permanently inactivates cholinesterases, yielding falsely low concentrations. Specimens for red blood cell cholinesterase are usually drawn into tubes containing a chelating anticoagulant such as ethylenediaminetetraacetic acid (EDTA) to prevent clot formation. Samples for butyrylcholinesterase do not require an anticoagulant and can be drawn into a tube without chelators or anticoagulants.

MANAGEMENT

Decontamination

The approach to patients with organic phosphorus and carbamate poisoning is identical. Those with serious or life-threatening toxicity should undergo initial treatment and decontamination simultaneously. Rapid cutaneous absorption necessitates removal of all clothing. Medical personnel should avoid contamination by wearing appropriate protective equipment. Skin should be washed repeatedly with water and soap. Cutaneous absorption can also occur as a result of contact with vomitus and diarrhea if the initial exposure was through ingestion. Oily insecticides may be difficult to remove from thick or long hair, even with repeated shampooing, and shaving scalp hair might be necessary. Some items, such as leather shoes, belts, and watchbands, cannot be decontaminated and should be discarded.

If emesis has not occurred following ingestion, evacuation of stomach contents is recommended by nasogastric lavage. Activated charcoal (1 g/kg) should be routinely given, unless contraindicated.

Supportive Care

The earliest causes of death are from respiratory failure from weakness or paralysis and from bronchorrhea. If adjuncts for endotracheal intubation are necessary, succinylcholine and mivacurium should be avoided as they are metabolized by butyrylcholinesterase and paralysis may be prolonged to 24 hours or more.

Antidotes

Atropine

The second priority in management is to control excessive muscarinic activity. Atropine sulfate competitively antagonizes ACh at muscarinic receptors to reverse excessive secretions, miosis, bronchospasm, vomiting, diarrhea, diaphoresis, and urinary incontinence. While initial doses should follow advanced cardiac life support (ACLS) or pediatric advanced life support (PALS) guidelines, serious poisoning can require as much as 1000 mg of atropine in 24 hours and total doses as large as 11,000 mg are reported during the course of treatment. As such, most clinicians use a doubling strategy (1, 2, 4, 8, 16 mg, etc.) every 3–5 minutes until atropinization is achieved. At some point, the use of continuous atropine infusions may be more convenient. The end point is drying of pulmonary secretions with little regard for pupils or heart rate. Because large doses of atropine may pro-

duce long-lasting delirium and exhaust supplies, glycopyrrolate (initial dose 1–2 mg) may be substituted; it offers the advantage of minimal CNS penetration.

Pralidoxime

Pralidoxime (2-PAM) acts to regenerate AChE. Because atropine cannot reverse nicotinic findings, 2-PAM is administered when either nicotinic toxicity is present or atropine doses exceed standard ACLS or PALS recommendations. Because the organic phosphorus compound–AChE ages (becomes permanent with time), it is essential to begin 2-PAM therapy as early as possible, when indicated.

The initial dose of pralidoxime in adolescents and adults is 2 g intravenously over 10–15 minutes (25–50 mg/kg IV to a maximum of the adult dose in children). Rapid infusion of 2-PAM should be avoided as it can exacerbate toxicity by transiently blocking AChE. When response to the initial dose is acceptable, 2-PAM should be continued every 6 hours until the patient remains asymptomatic for at least 24 hours. In more severe cases, a continuous infusion is started at 250–500 mg/h (10–20 mg/kg/h in children) and titrated to clinical effect. Again, treatment should be continued for at least 24 hours after symptoms resolve.

If intermediate syndrome occurs, confirmation of depressed cholinesterase activity should be obtained, and 2-PAM therapy should be initiated pending results.

Benzodiazepines

Based on animal models, diazepam may improve survival in victims of severe organic phosphorus pesticide poisoning. Its effect appears to be more than the simple termination of seizures. Standard dosing should be used in all intubated or seizing patients.

Pralidoxime

Pralidoxime is the only cholinesterase-reactivating agent currently available in the United States. Its only use is with atropine in the management of patients poisoned by organic phosphorus and carbamate pesticides. Administration should be initiated as soon as possible because of the aging associated with the organic phosphorous–cholinesterase bond, but pralidoxime may remain effective for days after an exposure. Continuous infusion is preferable to intermittent administration for patients with serious toxicity and a prolonged therapeutic course may be required.

PHARMACOLOGY

The positively charged quaternary nitrogen of pralidoxime is attracted to the negatively charged anionic site on the phosphorylated enzyme, bringing it in close proximity to the phosphorous moiety. Pralidoxime then exerts a nucleophilic attack on the phosphate moiety, successfully competing for it and releasing it from the acetylcholinesterase enzyme. This action liberates the enzyme and permits enzymatic function. Organic phosphorus compounds with small, substituted side chains are more easily reversed by oximes because of better steric positioning, allowing easier access to the oximes.

Early in vitro evidence suggested that the successful use of cholinesterase reactivators depended on administration within 24–48 hours of exposure to the organic phosphorus compounds. However, according to currently available information there is no absolute time limitation on reactivator function.

Pralidoxime is most efficacious at nicotinic sites, often improving muscle strength within 10–40 minutes of administration. Pralidoxime is synergistic with atropine and in addition liberates enzyme so that additional acetylcholine can be metabolized.

OTHER REVERSAL AGENTS

To improve the central effect of pralidoxime, the dihydropyridine derivative of pralidoxime was synthesized. This derivative, known as pro-2-PAM, acts as a "prodrug," or drug carrier, which allows passage through membranes such as the blood–brain barrier. Obidoxime (Toxogenin) is an oxime used outside the United States that contains two active sites per molecule and is considered by some to be more effective than 2-PAM for certain organic phosphorus compounds. It is more effective in reactivating acetylcholinesterase than is pralidoxime. The H series of oximes (named after Hagedorn) were developed to act against the chemical warfare nerve agents. These agents have superior efficacy against sarin, VX, and certain types of newer pesticides (eg, methyl-fluorophosphonylcholines). Unfortunately, they are less efficacious for traditional organic phosphorus insecticide poisoning, and their toxicity profile is inadequately defined.

PHARMACOKINETICS AND PHARMACODYNAMICS

Although ideal effective concentrations are not established, a minimal effective concentration of pralidoxime is often stated as 4 μg/mL. A dose of 10

mg/kg (IM or IV) to volunteers results in peak plasma concentrations of 6 μg/mL (reached 5–15 minutes after IM injection) and a plasma half-life of approximately 75 minutes. In a human volunteer study, an intravenous loading dose of 4 mg/kg over 15 minutes followed by 3.2 mg/kg/h for a total of 4 hours maintained pralidoxime serum concentrations greater than 4 μg/mL for 257 minutes. The same total dose, 16 mg/kg, administered over 30 minutes only maintained those concentrations for 118 minutes. These results support the use of continuous infusions when clinically feasible.

Autoinjector administration of 600 mg of pralidoxime chloride in an adult man (9 mg/kg) produced a concentration above 4 μg/mL at 7–16 minutes, a maximum plasma concentration of 6.5 μg/mL at about 28 minutes, and a half-life of 2 hours.

INDICATIONS

Pralidoxime should be administered to patients with suspected or confirmed exposure to organic phosphorous or carbamate insecticides and either any signs or symptoms of neuromuscular weakness or a significant atropine requirement (usually described as more than a typical age or weight based resuscitation dose of atropine).

DOSING AND ADMINISTRATION

The optimal dosage regimen for pralidoxime is unknown. Traditionally, the recommended initial adult dose is 1–2 g in 100 mL of 0.9% sodium chloride solution given intravenously over 15–30 minutes. The pediatric dose is 20–40 mg/kg up to a maximum of 2 g as a loading dose given intravenously over 30 minutes. These initial doses can be repeated in 1 hour if muscle weakness and fasciculations are not relieved. Alternatively, a loading dose followed by a continuous maintenance infusion has been reported to be safe and effective in a limited number of adults and children. One recommendation is to administer a loading dose of 25–50 mg/kg (up to a maximum dose of 2.0 g) followed via continuous infusion of 10–20 mg/kg/h, up to 500 mg/h. Serious poisoning may require a continuous infusion of 500 mg/h in adults, and 10–20 mg/kg/h, up to 500 mg/h, in children.

Depending on the severity of a nerve agent exposure, 1–3 injections with the autoinjector of both atropine and pralidoxime should be administered. The number of autoinjector doses administered to a child depends on the child's age and weight. For children ages 3–7 (13–25 kg), one autoinjector of atropine and one autoinjector of pralidoxime should be administered, which should result in a projected pralidoxime dose of 24–46 mg/kg. For ages 8–14 years, 2 autoinjectors of atropine and 2 autoinjectors of pralidoxime should be administered. These injections should result in a projected pralidoxime dose of 24–46 mg/kg. For patients older than 14 years of age, 3 autoinjectors of atropine and pralidoxime should be administered. For children younger than 3 years old during an emergency, one autoinjector of atropine and one of pralidoxime may be administered in accordance with a risk-to-benefit analysis.

DURATION OF TREATMENT

In most cases, pralidoxime is continued for a minimum of 24 hours after symptoms have resolved. Alternatively, if serial determinations of red blood cell cholinesterase activity can be obtained in a timely fashion, restoration of

a normal value seems a reasonable end point of therapy. In all cases, patients should be observed for the reappearance of toxicity after termination of pralidoxime. If symptoms return, therapy should be continued for a minimum of an additional 24 hours.

ADVERSE EFFECTS

At therapeutic doses, adverse effects are minimal and may not be evident unless plasma concentrations are exceptionally high. Transient dizziness, blurred vision, and elevations in diastolic blood pressure may be related to the rate of administration. Rapid IV administration has produced sudden cardiac and respiratory arrest as a consequence of laryngospasm and muscle rigidity.

USE IN PREGNANCY

Pralidoxime is listed as pregnancy category C.

AVAILABILITY

Pralidoxime chloride (Protopam) is supplied in 20-mL vials containing 1 g of powder, ready for reconstitution with sterile water for injection. Pralidoxime chloride is also available for IM administration by an autoinjector containing 600 mg of pralidoxime in 2 mL of sterile water for injection with 20 mg benzyl alcohol and 11.26 mg glycine. The 2-PAM autoinjector also comes packaged in a kit accompanied by an autoinjector containing 2 mg of atropine in 0.7 mL of a sterile solution containing 12.47 mg glycerin and not more than 2.8 mg phenol. This kit is called a "Mark 1 Nerve Agent Antidote Kit (NAAK)" and is designed to be used IM by first responders in case of a nerve agent attack.

Atropine

Atropine is the prototypical antimuscarinic drug. It is a competitive antagonist at both central and peripheral muscarinic receptors, that is used to treat symptomatic exposures to muscarinic agonists and acetylcholinesterase inhibitors such as organic phosphorous pesticides and organic phosphorus chemical warfare nerve agents.

CHEMISTRY

Atropine (*dl*-hyoscyamine), like scopolamine (*l*-hyoscine), is a tropane alkaloid with a tertiary amine structure that allows CNS penetration. Quaternary amine antimuscarinic agents, such as glycopyrrolate, ipratropium, and tiotropium, do not cross the blood–brain barrier into the CNS.

PHARMACOLOGY

Cholinesterase inhibitors (eg, organic phosphorous insecticides, chemical warfare nerve agents) prevent the breakdown of acetylcholine by acetylcholinesterase, increasing the amount of acetylcholine available to stimulate cholinergic receptors. Cholinergic receptors are made up of muscarinic and nicotinic receptors.

Muscarinic receptors are widely distributed throughout the peripheral and central nervous systems. They are coupled to G proteins and either inhibit adenylyl cyclase (M_2, M_4) or increase phospholipase C (M_1, M_3, M_5). Atropine is a competitive antagonist of acetylcholine primarily at muscarinic receptors (M_1–M_5). The duration of action of atropine is dose and route dependent and may last 24 hours or longer, depending on the particular end point being evaluated.

PHARMACOKINETICS AND PHARMACODYNAMICS

Atropine is absorbed rapidly from most routes of administration, including inhalation, oral, and IM. Oral ingestion of 1 mg of atropine produced maximal effects on heart rate and on salivary secretions at 1 and 3 hours respectively. The plasma concentrations of atropine are similar at 1 hour following either 1 mg IV or IM in adults. The IM administration of atropine by autoinjector significantly decreased the time to maximal effect when compared to IM administration by conventional needle and syringe. Following IM administration of 0.02 mg/kg in adults, the absorption rate and elimination rates were 8 minutes and 2.5 hours, respectively. Renal elimination accounts for 34–57% of the dose.

Ocular instillation of atropine causes mydriasis by blocking the M_3 muscarinic receptor on the iris sphincter muscle. The peak mydriatic effect occurs within 30–40 min and persists for 7–10 days. Ophthalmic atropine also causes cycloplegia by blocking the M_3 muscarinic receptor on ciliary muscle. Peak cycloplegia occurs within 1–3 hours and persists for 6–to 12 days.

An investigation of the oral bioavailability of atropine eye drops in healthy adults revealed, on average, 65% systemic absorption, but with a wide individual variability. The time to maximum serum concentration was 30 minutes and the elimination half-life was 2.5 hours. Given the short supply of parenteral atropine during a mass casualty event atropine eye drops may prove to be a useful substitute. Following inhalation the time to peak atropine concentration averaged 1.3 hours.

INDICATIONS

For the treatment of organic phosphorous and carbamate poisoning, atropine is used either alone or in combination with 2-PAM. Additional indications include poisoning by muscarine-containing mushrooms, cholinergic medications, and to a lesser extent, to reverse bradycardia induced by cardioactive steroids, β-adrenergic antagonists, and calcium channel blockers.

DOSAGE AND ADMINISTRATION

The dosage regimen of atropine for an organic phosphorous pesticide poisoning in adults has never been studied in a randomized controlled trial and there is considerable variation in recommendations. However, experience suggests that atropine should be initiated in adults in doses of 1–2 mg IV for mild to moderate poisoning and 3–5 mg IV for severe poisoning with unconsciousness. This dose can be doubled every 3–5 minutes as needed. The most important end point for adequate atropinization is clear lungs and the reversal of the muscarinic toxic syndrome. Once this end point has been achieved, a maintenance dose of atropine may need to be started. An additional approach is to administer 10–20% of the loading dose as an IV infusion every hour initially, with meticulous frequent reevaluation and titration.

ADVERSE EFFECTS AND TOXICITY

When too much atropine is administered, the patient demonstrates classic signs of peripheral anticholinergic toxicity: hot, dry, flushed skin, urinary retention, absent bowel sounds, tachycardia, mydriasis, and central anticholinergic activity, including restlessness, confusion, and hallucinations or CNS depression. In the absence of a cholinergic agent, these adverse effects begin at 0.5 mg IV in the adult. However, in the presence of a muscarinic agonist or an anticholinesterase agent, the effects may not occur until many milligrams of atropine are administered.

USE IN PREGNANCY

Atropine is classified by the FDA as pregnancy category C. Atropine crosses the placenta and may cause tachycardia in the near term fetus.

AVAILABILITY

Atropine sulfate injection (USP) is available in many different strengths, with the following concentrations in each 1-mL vial or ampule: 50 μg, 300 μg, 400 μg, 500 μg, 800 μg, and 1 mg. The AtroPen Auto-Injector is a prefilled syringe designed for IM injection by an autoinjector into the outer thigh. It is available in 4 strengths: 0.25 mg, 0.5 mg (Blue Label), 1 mg (Dark Red Label), and 2 mg (Green Label). Atropine is also packaged in a kit with a second autoinjector containing 600 mg of pralidoxime in 2 mL of sterile water for injection with 40 mg of benzyl alcohol and 22.5 mg of glycine. The atropine autoinjector contains 2 mg of atropine in 0.7 mL of a sterile solution containing 12.47 mg of glycerin and not more than 2.8 mg of phenol. This particular combination kit is called a “Mark 1 Nerve Agent Antidote Kit” (NAAK) and is designed for IM use in case of a nerve agent attack.

110 Insecticides: Organic Chlorines, Pyrethrins/ Pyrethroids, and DEET

ORGANIC CHLORINE PESTICIDES

History and Epidemiology

Until the 1940s, commonly available pesticides included highly toxic arsenicals, mercurials, lead, sulfur, and nicotine. The organic chlorine insecticides were developed as inexpensive, nonvolatile, environmentally stable, insecticides with relatively low acute toxicity. Widespread use of these compounds occurred from the 1940s until the mid-1970s. However, the properties that made them effective insecticides also made them environmental hazards: slow metabolism, lipid solubility, chemical stability, and environmental persistence. The demonstration of dichlorodiphenyltrichloroethane (DDT) residues in humans, led to the severe restriction or total ban of DDT and most other organic chlorines in North America and Europe. DDT is still widely used for malaria control programs in many countries.

Toxicokinetics

The organic chlorine pesticides are grouped into four categories based on their chemical structures and similar toxicities: (a) DDT and related analogs; (b) cyclodienes (the related isomers aldrin, dieldrin, and endrin, as well as heptachlor, endosulfan) and related compounds (toxaphene, dienochlor); (c) hexachlorocyclohexane (lindane, the γ isomer, with the commonly used misnomer γ-benzene hexachloride); and (d) mirex and chlordecone. These compounds differ substantially, both between and within groups, with respect to toxic doses, skin absorption, fat storage, metabolism, and elimination. The signs and symptoms of toxicity in humans, however, are remarkably similar within each group.

Absorption

All of the organic chlorine pesticides are well absorbed orally and by inhalation; transdermal absorption is variable, depending on the particular compound. DDT and its analogs are very poorly absorbed transdermally, unless the pesticide is dissolved in a suitable hydrocarbon solvent. DDT has limited volatility, so that air concentrations are usually low, and toxicity by the respiratory route is unlikely. All of the cyclodienes have significant transdermal absorption rates. Toxaphene is poorly absorbed through the skin in both acute and chronic exposures. Lindane is well absorbed after skin application. Mirex and chlordecone are efficiently absorbed via skin, by inhalation, and orally.

Distribution

All organic chlorines are lipophilic, a property that allows penetration to their sites of action. The fat-to-serum ratios at equilibrium are high, in the range of 660:1 for chlordane; 220:1 for lindane; and 150:1 for dieldrin.

Metabolism

The high lipid solubility and very slow metabolic disposition of DDT, DDE (dichlorodiphenyldichloroethylene, a metabolite of DDT), dieldrin, hep-

tachlor, chlordane, mirex, and chlordecone causes significant adipose tissue storage and increasing body burdens in chronically exposed populations. Organic chlorines that are rapidly metabolized and eliminated, such as endrin (an isomer of dieldrin), endosulfan, lindane, methoxychlor, dienochlor, chlorobenzilate, dicofol, and toxaphene, tend to have less persistence in body tissues, despite being highly lipid soluble.

Most organic chlorines are metabolized by the hepatic microsomal enzyme systems by dechlorination, oxidation, most with subsequent conjugation. In animals, most organic chlorine pesticides induce the hepatic microsomal enzyme systems. However, induction of hepatic enzymes has not been described in man, except in rare cases of massive exposure with concomitant neurologic findings.

Elimination

The half-lives of fat-stored compounds and poorly metabolized organic chlorines such as DDT and chlordecone are measured in months or years. The elimination half-life of lindane is 21 hours in adults. The primary route of excretion of the organic chlorines is in the bile, but most also have detectable urinary metabolites.

Mechanisms of Toxicity

The organic chlorines exert their most important effects in the central nervous system, where they affect the neuronal membrane by either interfering with repolarization, by prolonging depolarization, or by impairing the maintenance of the polarized state of the neuron. The end result is hyperexcitability of the nervous system and repetitive neuronal discharges. DDT primarily affects the axon, by causing the voltage-dependent Na^+ channels to remain open after depolarization, allowing repetitive action potentials. The cyclodienes, toxaphene and lindane act as γ-aminobutyric acid (GABA) antagonists.

Organic chlorines also sensitize the myocardium to endogenous catecholamines and predispose test animals to dysrhythmias, presumably in a fashion similar to the chlorinated hydrocarbon solvents (Chap. 102).

Drug Interactions

There are theoretical consequences of liver enzyme induction, such as enhanced metabolism of therapeutic drugs and/or reduced efficacy.

Clinical Manifestations

Acute Exposure

In sufficient doses, organic chlorines lower the seizure threshold (DDT and related sodium channel xenobiotics) or remove inhibitory influences (antagonism to GABA effects) and produce CNS stimulation, with resultant seizures, respiratory failure, and death. After DDT exposure, tremor may be the only initial manifestation. Nausea; vomiting; hyperesthesias of the mouth and face; paresthesias of face, tongue, and extremities; headache; dizziness; myoclonus; leg weakness; agitation; and confusion may subsequently occur. Seizures only occur after very high exposures, usually only after ingesting large amounts. Single, acute, oral doses of 10 mg/kg or more of DDT are usually necessary to produce symptoms. However, with lindane, the cyclodienes, and toxaphene, there often are no prodromal signs or symptoms, and more often than not, the first manifestation of toxicity is a generalized seizure. If sei-

zures develop, they often occur within 1–2 hours of ingestion when the stomach is empty, but may be delayed as much as 5–6 hours when the ingestion follows a substantial meal.

The cyclodienes are notable for their propensity to cause seizures that may recur for several days following an acute exposure. If the seizures are brief and hypoxia has not occurred, recovery is usually complete. Hyperthermia secondary to central mechanisms or increased muscle activity is common.

Lindane: Specific Risks

Patients are at risk for developing central nervous system toxicity from improper topical therapeutic use such as exceeding recommended application times or amounts, repeated applications, application following hot baths, and use of occlusive dressings or clothing after application. Toxicity also occurs after unintentional oral ingestion of topical preparations. Young children appear at greatest risk, possibly because of greater skin permeability, increased ratio of body surface area to mass, or immature liver enzymes.

Chronic Exposure

Chlordecone, unlike the other organic chlorines, produces an insidious picture of chronic toxicity related to its extremely long persistence in the body. The clinical syndrome consists of a prominent tremor of the hands, a fine tremor of the head, and trembling of the entire body. Other findings include weakness, opsoclonus (rapid, irregular, dysrhythmic ocular movements), ataxia, mental status changes, rash, weight loss, and elevated liver enzymes.

Diagnostic Testing

The history of exposure to an organic chlorine pesticide is the most critical piece of information. Toxaphene, a chlorinated pinene, has a mild turpentine-like odor, and endosulfan has a unique, "rotten egg," sulfur odor.

Gas chromatography can detect organic chlorine pesticides in serum, adipose tissue, and urine. Laboratory evaluation will not alter the course of management, as these blood tests are not available on an emergent basis. At present, there are no data correlating health effects and tissue concentrations. Most humans studied have measurable concentrations of DDT in adipose tissue. Serum lindane levels document exposure, and most laboratories report toxic ranges. Lindane-exposed workers with chronic neurologic symptoms showed blood lindane concentrations of 0.02 mg/L. A limited series of patients with acute lindane ingestion suggests that a serum concentration of 0.12 mg/L correlates with sedation, and that 0.2 mg/L is associated with seizures and coma.

Management

As with any patient who presents with an altered mental status, assessment and stabilization of the airway is necessary, followed by administration of dextrose and thiamine as indicated. Skin decontamination is essential, especially in the case of topical lindane. Clothing should be removed and placed in a plastic bag and the skin washed with soap and water. Healthcare providers should be protected with rubber gloves and aprons. Because these pesticides are almost invariably liquids, a nasogastric tube can be used to suction and lavage the gastric contents, if clinically indicated. This is most appropriate only with a very recent ingestion (Chap. 8). Because the organic chlorines are all neurotoxins, the risk

of complications associated with seizures probably outweighs the risk of any of the GI decontamination strategies once toxicity is evident.

Seizures should be controlled with a benzodiazepine followed by pentobarbital or a propofol infusion and neuromuscular blockade, if necessary. Phenytoin is much less effective in these cases, particularly with the GABA-chloride ionophore antagonists lindane, toxaphene, and the cyclodienes. Hyperthermia should be managed aggressively with external cooling. Cholestyramine, at a dosage of 16 g/d in divided doses, should be administered to all patients symptomatic from chlordecone, and possibly other organic chlorines.

Pyrethrins and Pyrethroids

The pyrethrins are the active extracts from the flower *Chrysanthemum cinerariaefolium.* Pyrethrum, the first pyrethrin identified, consists of 6 esters derived from chrysanthemic acid and pyrethric acid. When applied properly, they have essentially no systemic mammalian toxicity because of their rapid hydrolysis. Pyrethrins break down rapidly in light and in water, and therefore have no environmental persistence or bioaccumulation.

The pyrethroids are the synthetic derivatives of the natural pyrethrins. They were developed in an effort to produce more environmentally stable products. There are more than 1000 pyrethroids, of which 6–10 are in widespread use today. These insecticides have a rapid paralytic effect ("knock down") on insects. The classification of pyrethroids is based on their structure, their clinical manifestations in mammalian poisoning, as well as their actions on insect nerve preparations and their insecticidal activity. Type I pyrethroids have a simple ester bond at the central linkage without α cyano group. The type II pyrethroids have α cyano group at the α carbon of this ester linkage. The α cyano group greatly enhances neurotoxicity of the type II pyrethroids and they are generally considered more potent and toxic than the type I pyrethroids (Table 110–1).

Toxicokinetics

Absorption

The oral toxicity of pyrethrins in mammals is extremely low, because they are so readily hydrolyzed into inactive compounds. Their dermal toxicity is even lower, owing to their slow penetration and rapid metabolism. The pyrethroids are more stable than the natural pyrethrins, and systemic toxicity occurs following ingestion. Direct absorption of pyrethroids through the skin to the peripheral sensory nerves occurs. The pyrethroids are also absorbed via inhalation, but not to a clinically significant degree.

Distribution

The pyrethroids and pyrethrins are lipophilic and as such are rapidly distributed to the central nervous system.

Metabolism

The pyrethroids are readily metabolized in animals and humans by hydrolases and the cytochrome P450-dependent microsomal system. The metabolites are of lower toxicity than the parent compounds. Piperonyl butoxide, a P450 inhibitor, enhances the potency of pyrethroids. It is often added to insecticide preparations to ensure lethality, as the initial "knock down" effect of a pyrethroid alone is not always lethal to the insect.

TABLE 110-1. Synthetic Pyrethroids in Common Use

Pyrethroid Class	Generic Name, CAS #	Brand Names	Generation of Pyrethroid, Dates Introduced (If Available)
Type I	Allethrin 584-79-2	Pynamin	1st generation; First synthetic pyrethroid, 1949
	Bioallethrin 584-79-2	D-trans	2nd generation, 1969: trans isomer of allethrin
	Dimethrin 70-38-2	Dimetrin	
	Phenothrin 26002-80-2	Fenothrin, Forte, Sumithrin	2nd generation, 1973
	Resmethrin 10453-86-8	Benzofluroline, Chrysron, Crossfire, Premgard, Pynosect, Pyretherm, Synthrin	2nd generation, 1967; 20× strength of pyrethrum
	Bioresmethrin 28434-01-7		2nd generation, 1967; 50× strength of pyrethrum, isomer of resmethrin
	Tetramethrin 7696-12-0	Neo-Pynamin	2nd generation, 1965
	Permethrin 52645-53-1	Ambush, Biomist, Dragnet, Ectiban, Elimite, Ipitox, Ketokill, Nix, Outflank, Perigen, Permasect, Persect, Pertox, Pounce, Pramex, etc	3rd generation, 1972; Effective topical scabicide & miticide, low toxicity
	Bifenthrin 82657-04-3	Capture, Talstar	4th generation
	Prallethrin 23031-36-9	SF, Etoc	4th generation
	Imiprothrin 72963-72-5	Multicide, Pralle, Raid Ant & Roach	4th generation; 1998
Type II	Fenvalerate 51630-58-1	Belmark, Evercide, Extrin, Fenkill, Sanmarton, Sumicidin, Sumifly, Sumipower, Sumitox, Tribute	3rd generation, 1973
	Acrinathrin 103833-18-7	Rufast	4th generation
	Cyfluthrin 68359-37-5	Baythroid, Bulldock, Cyfoxylate, Eulan SP, Solfac, Tempo 2	4th generation
	Cyhalothrin 91465-08-6	Demand, Karate, Ninja 10WP, Scimitar, Warrior	4th generation

Cypermethrin 52315-07-8	Ammo, Barricade, CCN52, Cymbush, Cymperator, Cynoff, Cypercopal; Cyperkill, Cyrux, Demon, Flectron, KafilSuper, Ripcord, Siperin, others	4th generation
Deltamethrin 52918-63-5	Butoflin, Butox, Crackdown, Decis, DeltaDust, DeltaGard, Deltex, K-Othrine, Striker, Suspend	4th generation
Esfenvalerate 66230-04-4	Asana, Asana-XL, Sumi-alpha	4th generation
Fenpropathrin 39515-41-8	Danitol, Herald, Meothrin, Rody	4th generation, 1989
Flucythrinate 70124-77-5	AASTAR, Cybolt, Fluent, Payoff	4th generation
Fluvalinate 102851-06-9	Evict, Fireban, Force, Mavrik, Raze, Yardex	4th generation
Tefluthrin 19538-32-2	Demand, Force, Karate, Scimitar	4th generation
Tralomethrin 66841-25-6	Dethmor, SAGA, Scout, Scout X-tra, Tralex	4th generation

Elimination

There is no evidence that the pyrethroids undergo enterohepatic recirculation. Parent compounds, as well as metabolites of the pyrethroids, are found in the urine.

Pathophysiology

Like DDT, pyrethrins and pyrethroids prolong the activation of the voltage-dependent sodium channel by binding to it in the open state, causing a prolonged depolarization (Chap. 14). This effect on voltage-sensitive sodium channels is responsible for the insecticidal activity, as well as the toxicity of the pyrethroids to nontarget species. Type II pyrethroids are more potent, and lead to significant after-potentials and eventual nerve conduction block. Additionally, pyrethroids block voltage-sensitive chloride channels, which may enhance CNS toxicity.

Clinical Manifestations

Most cases of toxicity associated with the pyrethrins are the result of allergic reactions. At highest risk are patients who are sensitive to ragweed pollen. The synthetic pyrethroids generally do not induce allergic reactions. The type I pyrethroids are unlikely to cause systemic toxicity in humans. The type II pyrethroids cause paresthesias, salivation, nausea, vomiting, dizziness, fasciculations, altered mental status, coma, seizures, and acute lung injury. Many of the findings resemble organic phosphorus compound overdose. Most exposures are dermal, and local symptoms predominate in the majority of cases. The predominant feature is local paraesthesias in the areas of contact. Ocular contact causes more severe symptoms, including immediate pain, lacrimation, photophobia, and conjunctivitis.

Treatment

Initial treatment should be directed toward skin decontamination, as most poisonings occur from exposures by this route. Patients with large oral ingestions of a type II pyrethroid should be treated with a single, standard dose of activated charcoal, unless the diluent of the pyrethroid contains a petroleum solvent. Contact dermatitis and acute systemic allergic reactions should be treated in the usual manner, using antihistamines, corticosteroids and β-adrenergic agonists as clinically indicated.

Treatment of systemic toxicity is entirely supportive and symptomatic, because no specific antidote exists. Benzodiazepines should be used for tremor and seizures.

DEET

The topical insect repellant, *N*,*N*-diethyl-3-methylbenzamide (DEET, former nomenclature *N*,*N*-diethyl-*m*-toluamide), was patented by the US Army in 1946, and commercially marketed in the United States since 1956 as a mosquito repellant. The U.S. Environmental Protection Agency (EPA) estimates that 38% of the U.S. population uses DEET each year. DEET can be purchased in multiple formulations without prescription in concentrations ranging from 5–100%.

Toxicokinetics

DEET is extensively absorbed via the gastrointestinal tract. Skin absorption is significant, depending on the vehicle and the concentration. The volume of

distribution is large, in the range of 2.7–6.21 L/kg in animal studies. DEET is extensively metabolized by oxidation and hydroxylation by the hepatic microsomal enzymes, primarily by the isozymes CYP2B6, CYP3A4, CYP2C19, and CYP2A6. DEET is excreted in the urine within 12 hours, mainly as metabolites, with 15% or less appearing as the parent compound.

Pathophysiology

The exact mechanism of DEET toxicity is unknown.

Clinical Manifestations

Most calls to poison control centers regarding DEET exposures involve minor or no symptoms, and symptomatic exposures occur primarily when DEET is sprayed in the eyes or inhaled. A recent review of adverse reactions to DEET showed 26 cases had major morbidity including encephalopathy, ataxia, convulsions, respiratory failure, hypotension, anaphylaxis, or death, particularly after ingestion or dermal exposure to large amounts. These adverse reactions occurred mainly in children, and most involved prolonged use and dosages exceeding recommendations.

Treatment

Most symptoms resolve without treatment and the majority of patients with serious toxicity recover fully with supportive care. In cases of dermal exposures, skin decontamination should be a priority to prevent further absorption. Patients with intentional oral ingestions should receive a single dose of activated charcoal if clinically indicated. Seizures should be treated as discussed above.

111 Herbicides

HISTORY AND EPIDEMIOLOGY

Herbicides are chemicals intended to kill unwanted vegetation or regulate some aspect of the growth cycle of plants. In the late 1800s, farmers had few options for weed control. Smothering weeds before planting by turning the soil with a plough was a standard agricultural practice that only recently is being replaced with an alternative "no-till" practice. The first serious attempts to find chemicals for weed control culminated in the success of Bordeaux mixture (copper sulfate and lime) and Paris Green (copper acetoarsenite) in controlling fungal diseases affecting the French vineyards. In the 1940s the first herbicidal chemical based specifically on plant physiology was discovered, 2,4-dichlorophenoxyacetic acid (2,4-D). The period since the 1940s has been characterized by the steady introduction of a large number of active herbicides into the marketplace. Over 200 chemicals are currently registered for use as herbicides in the United States and approximately 500 chemicals are in use worldwide. The highest-use agricultural herbicides in pounds in 2001 were glyphosate, 88 million pounds; atrazine, 77 million pounds; metolachlor, 41 million pounds; acetochlor, 33 million pounds; and 2,4-D, 31 million pounds.

Because of the nature of the commercial herbicide industry, active ingredients and different salts are introduced, combined in a nearly endless series of product formulations and names, and then withdrawn from the market. Formulations also vary by country. Risk of toxicity depends on the amount and concentration of active ingredient and formulation adjuvants in the preparation to which the patient was actually exposed.

PARAQUAT

Because of its low cost, rapid action, and favorable environmental characteristics, paraquat remains a widely used herbicide throughout the world. The combination of ready availability and severe toxicity results in serious and fatal poisonings.

Paraquat dichloride is marketed most commonly as an aqueous solution concentrate containing 200 g paraquat dichloride/L (20% weight/volume [w/v]), sometimes in combination with diquat or other herbicides. The aqueous concentrates also contain appropriate adjuvants as described above and sometimes deterrent adjuvants to prevent or mitigate unintentional ingestion. If no blue dye is added, the concentrate is colored dark brown like cola, for which it can be mistaken, especially if decanted into a soft drink bottle.

Most cases of paraquat poisoning result from deliberate ingestion. Unintentional ingestions can occur, particularly when the product has been handled or stored incorrectly. Death has also been reported from homicidal use, massive dermal exposure, intravenous administration, and prolonged occupational spraying.

Toxicokinetics

Absorption

Splash or diluted spray mist exposure to skin, eyes, and upper airways leads to minimal systemic absorption despite the risk of local tissue damage. Dermal expo-

sure to burned skin and chronic occupational exposure have resulted in sufficient paraquat absorption to cause death. Following ingestion, systemic absorption of paraquat is rapid but incomplete (<30% of the dose). Peak plasma concentrations of paraquat generally occur within 2 hours after ingestion. The volume of distribution of paraquat is about 1–2 L/kg. It distributes rapidly to most tissues, with highest concentrations in the kidneys and the lungs. Higher renal concentrations reflect the role of the kidney in the elimination of paraquat. The high concentrations in the lung result from time- and energy-dependent uptake of paraquat by type I and II alveolar epithelial cells via the polyamine uptake pathway.

Elimination

More than 90% of the absorbed dose of paraquat is eliminated by the kidneys as the parent compound within the first 12–24 hours after the ingestion. As renal function deteriorates as a result of the poisoning, clearance of paraquat falls concurrently, and the half-life becomes prolonged, from about 12 hours to more than 24 hours.

Mechanism

The mechanism of toxicity has been determined most clearly in the lung where paraquat is reduced by a nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reaction to the mono-cation radical. This radical spontaneously reacts with molecular oxygen to form a superoxide radical as well as regenerating the original paraquat di-cation, which now can undergo the oxidation–reduction (redox) cycle again. The nearly inexhaustible supply of electrons and oxygen in the lung sustain this redox cycling. Damage to other organs, such as kidney, heart, liver, pancreas, and muscle, is assumed to be related to redox cycling and oxygen toxicity, but this has not been proven.

Clinical Manifestations

Table 111–1 summarizes the clinical features of paraquat poisoning. The severity and course of paraquat ingestion poisoning can be divided into three categories that broadly reflect dose-response. *Mild–moderate* poisoning usually results from an ingestion of 10 mL or less of 20% paraquat dichloride concentrate in an adult, equivalent to 20 mg paraquat cation or 28.6 mg paraquat dichloride salt. Recovery is expected and is complete. *Moderate–severe* poisoning occurs in patients who ingest 20–40 mg paraquat cation/kg (10–20 mL of the 20% concentrate). They characteristically exhibit early development of upper GI tract corrosion, acute renal tubular necrosis, and hepatic injury. CNS involvement may appear as headache, dizziness, drowsiness and incoordination, and coma. Respiratory failure may be accompanied by patchy infiltrates, which appear on the chest radiograph. Patients generally survive the acute phase and experience delayed but progressive pulmonary inflammation, fibrosis, and profound hypoxemia, which is the cause of death. Mortality occurs 5 days to several weeks after the ingestion. A *fulminant* course of poisoning occurs in patients who ingest more than 40 mg paraquat cation/kg (>20 mL of 20% concentrate) in an adult. They do not survive long enough to demonstrate pulmonary fibrosis. Patients exhibit severe vomiting and diarrhea, oropharyngeal and gastrointestinal ulceration, renal and hepatic failure, acute pulmonary injury and alveolitis, cardiac dysrhythmias, shock, and coma. They usually die within 1–4 days after ingestion from multiorgan failure.

TABLE 111–1. Clinical Features of Paraquat Poisoning by Organ System

Cardiovascular Hypovolemia, shock, dysrhythmias	**Genitourinary** Oliguric or nonoliguric renal failure caused by acute tubular necrosis; proximal tubular dysfunction
Central nervous Coma, convulsions, cerebral edema	**Hematopoietic** Leukocytosis early, anemia late
Dermatologic Corrosion of skin, nails, cornea, conjunctiva, and nasal mucosa	**Respiratory** Cough, aphonia, prominent pharyngeal membranes (pseudodiphtheria), mediastinitis, pneumothorax, hemoptysis, acute lung injury, hemorrhage, pulmonary fibrosis
Endocrine Adrenal insufficiency caused by adrenal necrosis as part of multiple organ failure	
Gastrointestinal Oropharyngeal ulceration and corrosion; nausea, vomiting, hematemesis, diarrhea, dysphagia, perforation of esophagus, pancreatitis, centrilobular hepatic necrosis, cholestasis	

Diagnostic Testing

Plasma or urine paraquat concentrations can be measured quantitatively by a variety of techniques, but quantitative assay results are not available in a timely manner to assist with management of the patient. Rapid, qualitative analysis in urine is performed by reducing paraquat to its blue mono-cation radical with sodium dithionite under alkaline conditions and comparing the result with appropriate positive and negative controls. If paraquat is present in a concentration of ≥2 μg/mL, a concentration-dependent blue-to-black color is evident.

Management

Early treatment is a very important determinant of survival in paraquat-poisoned patients. If there has been dermal exposure, either primarily or secondarily from contact with contaminated vomitus, the clothing should be removed immediately and the skin washed gently but thoroughly with soap and water. If the eyes have been splashed, ocular irrigation with copious amounts of water should continue for 15 minutes.

Gastric Emptying

If paraquat was ingested only minutes earlier, measures to remove it or prevent its absorption from the gastrointestinal tract should be instituted immediately. Spontaneous vomiting is a near certainty in significant ingestions because of both the irritant effects of paraquat and the emetic added to many formulations. Naso- or orogastric lavage may have applicability only in patients who present immediately after ingestion. Even if the patient has already vomited, further gastrointestinal decontamination should be considered. A slurry of activated

charcoal, Fuller earth, bentonite, or garden clay can be given. If the patient vomits the first dose of the adsorbent, another should be given, through a nasogastric tube if necessary. Rapid control of repeated vomiting with antiemetics and promotility agents is essential when the patient cannot retain the adsorbent.

Extracorporeal Removal

Methods to maintain or increase the rate of elimination of paraquat from the body should be considered. Hemoperfusion across a cartridge containing activated charcoal enhances elimination of paraquat from the blood. Although significant reduction in mortality can be demonstrated in dogs 2–12 hours after an LD_{50} or LD_{100} (median lethal dose for 50% and 100% of test subjects, respectively) dose of paraquat, there is no clinical evidence that hemoperfusion is efficacious in humans. Charcoal hemoperfusion should only be considered if it can be initiated *within 4 hours* of ingestion and continued for 6–8 hours. Hemodialysis should only be considered for paraquat removal when hemoperfusion is not available.

Supportive Care

Supportive and palliative care are the most important components of the management of paraquat-poisoned patients. Fluids and electrolytes should be administered IV in sufficient volume to replace GI tract losses and maintain normal hemodynamics and high-normal urine output. Analgesia may be needed for the pain associated with the mucosal ulceration. Patients should be monitored frequently for the development and progression of renal and respiratory failure. Supplemental oxygen is a double-edged sword in that it accelerates paraquat-induced oxygen radical toxicity as it temporarily relieves the distress of hypoxia. Generally, supplemental oxygen should be withheld until the arterial oxygen tension falls below 50 mm Hg and/or the patient expresses respiratory distress.

Lung transplantation has been performed in a few patients, but only one survivor is reported in the literature.

Prognosis

Plasma concentrations of paraquat measured within 28 hours after the ingestion are useful in estimating the prognosis according to the nomogram (Fig. 111–1). This nomogram was derived empirically from clinical data and not by statistical means. When experience with the nomogram was reviewed in 166 cases, it correctly predicted the outcome in 93% of patients who died and in 64% of those who survived. It appears that whenever the initial plasma concentration of paraquat exceeds 3 mg/L, mortality is 100%. The mode of death is cardiogenic shock within 24 hours of the ingestion in those whose paraquat concentrations exceed 10 mg/L.

DIQUAT

Diquat is used agriculturally for the same purposes as paraquat, as well as for the control of aquatic weeds. It is sometimes combined with paraquat. Recently, it has also been combined in dilute formulations with glyphosate to provide complementary herbicidal actions of rapid burn-down and elimination of viable root remnants. Diquat is similar to paraquat in terms of acute oral toxicity as measured by LD_{50} in rats (150–250 mg/kg), caustic local effects, kinetics, and mechanism of toxicity, with one important exception: Diquat lacks the structural features nec-

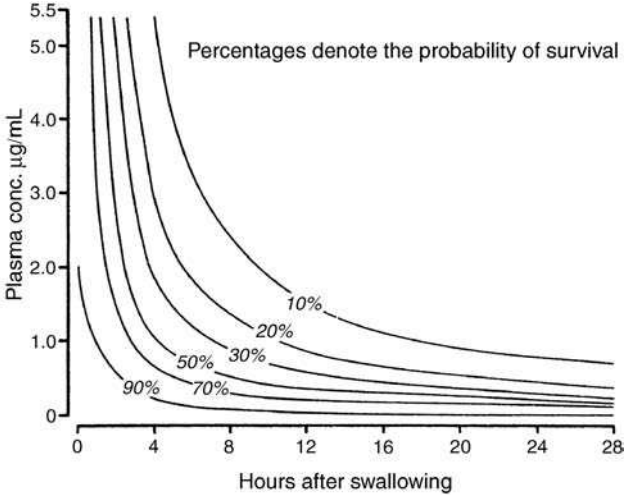

FIG. 111–1. Nomogram showing the relationship among the plasma concentrations of paraquat on the ordinate (µg/mL), time after ingestion on the abscissa, and the probability of survival. *(Reprinted with permission from Hart RB, Nevitt A, Whitehead A: A new statistical approach to the prognostic significance of plasma paraquat concentrations [Letter]. Lancet 1984;2:1222–1223.)*

essary for active transport by the polyamine uptake pathway into the lungs. Consequently, the extent of pulmonary injury and fibrosis following the ingestion of toxic doses of diquat is much less than that of paraquat. Instead, the predominant target organ is the kidney. Ingestion of diquat rapidly causes nausea, vomiting, watery diarrhea, and pain as a consequence of severe irritation or ulceration of the oropharynx, esophagus, and gastrointestinal tract. Local effects of dermal exposure include chemical burn and injury to nail beds. Skin exposure has been experimentally shown to be capable of causing systemic poisoning and death in experimental animals.

Treatment of diquat-exposed patients is similar to the treatment provided to those exposed to paraquat and includes gastric decontamination, adsorbents, hemodialysis or hemoperfusion, and supportive care. Extracorporeal removal techniques remove diquat from the circulation as renal failure ensues, but they have not appeared to affect mortality among the small number of reported cases.

GLYPHOSATE

Glyphosate is the classic example of an active ingredient of low human toxicity that is formulated and sold with other, more toxic ingredients that are primarily responsible for the acute health effects. Thus human toxicity of glyphosate formulations is not dependent on the glyphosate content primarily, but on the type and concentration of the surfactant, the preservative, the salt partner of glyphosate, and other adjuvants.

Mechanism of Toxicity of Glyphosate and Formulations

The glyphosate molecule itself has a relatively favorable acute toxicity profile in animals. Its acute oral toxicity is relatively low (rat oral LD_{50} = 5600 mg/kg). Because of the selective toxicity of glyphosate to plant life and corresponding low mammalian toxicity, the surfactant is suspected to be the primary culprit of the toxic syndrome. Many of the clinical features identified in glyphosate-surfactant poisonings occur regularly with reported cases of large volume ingestion of other herbicide concentrates irrespective of the active ingredient. The common factor is the presence of surfactant. Findings typically include superficial necrosis of mucous membranes, severe GI tract irritation with erosions, glottic edema, acute lung injury, profound hypotension, oliguria, renal failure, and cardiovascular collapse. In dogs, both the glyphosate–surfactant combination and surfactant alone cause hypotension through myocardial depression.

Clinical Manifestations

The range of clinical effects produced by ingestion of the original glyphosate formulation include irritation, edema, and erosions of the oropharynx and GI tract; nausea, vomiting, diarrhea, and chest and abdominal pain; leukocytosis, metabolic acidosis, elevated salivary amylase, tachypnea, hypoxia, acute lung injury, and volume responsive hypotension followed by hypotension unresponsive to fluids and vasopressors. Secondary organ dysfunction may occur in the CNS, liver, and kidneys.

Oral and gastrointestinal irritation (burning of mouth and throat, vomiting, abdominal pain) develop rapidly after ingestion. Hypotension may develop within hours of very large ingestions. Some patients may appear to be relatively stable for the first 8–12 hours and then develop hypotension and respiratory distress.

Those who ingest large volumes of highly concentrated herbicide (>200 mL of 41% glyphosate isopropylamine and ≥15% surfactant) and those who develop acute lung injury or cardiogenic shock are at greater risk of a fatal outcome. In one large series, there were 11 (27%) fatalities among 41 cases of patients who ingested an estimated 150 mL or more of concentrated formulation, but none among 51 patients who ingested <150 mL. In another large series, an average ingestion of 17 ± 16 mL (range: 5–50 mL) produced no symptoms; 58 ± 52 mL (range: 5–150 mL), produced mild symptoms; 128 ± 114 mL (range: 20–500 mL), produced moderate symptoms; and 184 ± 70 mL (range: 85–200 mL), produced severe symptoms or death.

Laboratory

In some fatal cases, serum glyphosate concentrations have been reported to exceed 3000 mg/L, although many are significantly lower. However, serum concentrations are not useful clinically in assessing the severity of exposure or poisoning. Furthermore, glyphosate concentrations are not readily available. Surfactant analysis is not feasible.

Treatment

After significant ingestions of herbicide concentrate, spontaneous vomiting usually occurs rapidly and obviates the need for the induction of emesis or lavage. Activated charcoal adsorbs the principal toxic component in formulated herbi-

cide, whether it is glyphosate, the surfactant, or both. It is not expected that hemodialysis would remove surfactant because of its large molecular size. There are no specific therapies or antidotal measures for glyphosate-surfactant poisoning.

2,4-D AND CHLOROPHENOXY HERBICIDES

Characteristics

2,4-D is the prototype and representative of a large group of related agents including diclofop, MCPA (methyl chlorophenoxy acetic acid), MCPB (methyl chlorophenoxy butyric acid), MCPP (mecoprop, methyl chlorophenoxy propionic acid), and silex.

Toxicokinetics

Absorption

Under experimental conditions, 2,4-D is rapidly and nearly completely absorbed after ingestion (>90%). Peak tissue concentrations occur in 4–12 hours. 2,4-D is poorly absorbed through the skin.

Distribution

Experimentally, 2,4-D appeared in brain tissue within 30 minutes of administration, and toxicity occurred concurrently. 2,4-D is highly protein bound.

Elimination

2,4-D is excreted in the urine mainly unchanged, with only a few percent found as a conjugated metabolite. The terminal elimination half-life is approximately 33 hours, but shortens with alkalinization of urine pH.

Mechanism of Toxicity

The toxic mechanisms of chlorophenoxy compounds in humans and animals are not understood but they appear to have multiple effects in biologic systems. These compounds are false substrates of both acetyl-coenzyme A synthase and choline acetyltransferase, false cholinergic messengers at nicotinic and muscarinic receptors, and weak uncouplers of oxidative phosphorylation.

Clinical Manifestations

2,4-D is severely irritating to the eyes, but not the skin. Most of the symptoms of chlorophenoxy poisoning appear to be in the central nervous system and the neuromusculature. Ingestion produces rapid onset of oral and gastrointestinal distress characterized by burning pain in mouth, throat and esophagus/chest, nausea, and vomiting that may persist for 12 or more hours, dysphagia, and diarrhea. Patients may then develop hypotension; tachypnea; tachycardia or tachydysrhythmias; fever; diaphoresis; metabolic acidosis; flushing; dizziness; lethargy; confusion; ataxia; and in severe poisoning, seizures or coma. Direct cardiac effects are suggested by various ECG changes and dysrhythmias; ventricular fibrillation is often the terminal event experimentally. Peripheral neuromuscular effects have included increased or decreased reflexes, hypotonia, weakness, muscle aching and tenderness, and fibrillatory twitching.

Laboratory

Analysis of biologic specimens for chlorophenoxy herbicide is not readily available and not needed for managing the patient. Similarly to salicylic acid,

another organic acid uncoupler of oxidative phosphorylation, sufficiently high doses may produce complex acid–base disturbances that include one or more elements of respiratory alkalosis and metabolic acidosis.

Management

Treatment consists of removing herbicide from the body and supportive care. Activated charcoal may be considered in significant ingestions. Limited evidence supports the use of urinary alkalinization to enhance the excretion of chlorophenoxy herbicides. Hemodialysis may be an option in severely poisoned patients.

GLUFOSINATE AND BIALAPHOS

Description

The soil fungus *Streptomyces hygroscopicus* produces the tripeptide phosphinothricin-alanine-alanine, also known as bialaphos, and this is metabolized in plants and animals to phosphinothricin, also known as glufosinate. Glufosinate is an analog of glutamic acid.

Toxic Mechanism

Glufosinate inhibits mammalian glutamine synthetase in various tissues and causes accumulation of ammonia and glutamate only when administered at near-lethal concentrations. Glufosinate also inhibits glutamate decarboxylase, leading to a decrease in γ-aminobutyric acid (GABA). Glufosinate and bialaphos are centrally neurotoxic in humans. Both seizures and profound CNS depression can occur concurrently. Clinical improvement lags behind the physical elimination of the compound, implying prolonged effect at the target site(s).

Toxicokinetics

Glufosinate and bialaphos are partially absorbed orally. Onset of serious CNS symptoms is delayed many hours to more than a day after a large volume ingestion of herbicide concentrate. Glufosinate is excreted renally unchanged. The distribution half-life is 1.84 hours and the elimination half-life is 9.6 hours. The apparent volume of distribution is estimated to be 1.4 L/kg. Renal clearance is 78 mL/min, and represents nearly all of the whole-body clearance.

Clinical Manifestations

Early symptoms of the systemic surfactant syndrome may appear very soon after ingestion of concentrate and include oral irritation, nausea and vomiting. Death from cardiovascular failure has occurred in at least two patients who ingested at least 300 mL of the surfactant-formulated herbicide. Onset of CNS symptoms is delayed for 4–8 hours after large ingestion; with significant symptoms such as coma and respiratory depression usually delayed for 24 hours or longer. CNS symptoms may continue to progress for 24–48 hours. Typical CNS symptoms include drowsiness, ataxia, disconjugate gaze, disorientation, tremor, stupor, deep coma, and central apnea and respiratory arrest. Seizures are a late manifestation of poisoning and appear in only approximately 50% of those seriously poisoned.

During the recovery period, the patient may experience loss of short-term memory (both retrograde and anterograde amnesia). This effect is also a feature of amnestic shellfish poisoning, which involves domoic acid, another excitatory amino acid neurotransmitter.

Laboratory

There is no readily available laboratory test to document ingestion of glufosinate or bialaphos or determine serum concentrations.

Management

Gastric Decontamination

Orogastric or nasogastric lavage and activated charcoal may be indicated for particular patients with substantial exposures. Spontaneous vomiting commonly occurs after significant ingestions of formulated herbicides because of the surfactant content; and may therefore make it unnecessary to attempt gastric lavage. Particular attention must be exercised in protecting the airway because of the obtundation and coma that may develop many hours after ingestion.

Extracorporeal Removal

Hemodialysis is superior to charcoal hemoperfusion in eliminating glufosinate from blood in vitro. However, several clinical authorities perform both procedures in tandem in an herbicide-poisoned patient. Improved clinical outcome has not been demonstrated for this practice. Early hemodialysis/hemoperfusion resulting in documented significant reductions in plasma glufosinate concentrations, failed to avert the progression of CNS pathology or hasten recovery.

Supportive Care

Prophylactic intubation is indicated for any glufosinate- or bialaphos-poisoned patient who becomes stuporous. Patients should be carefully monitored for adequate organ perfusion, respiratory effort, and oxygenation. Seizures respond to intravenous benzodiazepines. A single case of diabetes insipidus responded to intranasal desmopressin.

NITROPHENOLIC HERBICIDES

Dinitrophenol (DNP) and substituted nitrophenolic compounds (binapacryl, dinitrocresol [DNOC] and salts, dinoterb, dinoterbon, dinoseb and salts, dinofenate) inhibit cellular energy production in plants, fungi, and insects as the basis for their use as herbicides, miticides, fungicides and wood preservatives. 2,4-Dinitrophenol is the prototype and classic example of an agent that uncouples oxidative phosphorylation. There are no current registrations for any of these compounds for any pesticidal purpose in the United States, although opportunity for exposure still exists in other parts of the world, through leftover products, and through environmental contamination in some unremediated chemical waste sites (Chap. 39 for more discussion of DNP).

Sodium Chlorate ($NaClO_3$)

Chlorate is the chlorine analog of nitrate and kills all green plants by oxidizing and inactivating a critical nitrate reductase complex. Although not itself combustible, it reacts violently with reducing and combustible materials such as

clothing, wood, and dried foliage. Formulations usually carry a fire suppressant such as urea or sodium borate to counter this fire hazard. Sodium chlorate is sold alone or in combination with atrazine, 2,4-D, bromacil, diuron, or sodium metaborate. Minor amounts are also produced when chlorine dioxide is used to disinfect drinking water (Chap. 98 for more discussion on chlorates).

ATRAZINE AND OTHER CHLOROTRIAZINES

The chloro-S-triazine herbicides, including atrazine, simazine, cyanzine, and others, comprise one of the most extensively used herbicide class in the United States. Liquid formulations are likely to contain a hydrocarbon solvent. There are few reports of acute human toxicity.

Kinetics and Clinical Effects

The chlorotriazines are slowly and incompletely absorbed through skin: experimentally less than 5% in 20 hours, but are well absorbed orally (80%). Metabolism is by cytochrome P450 and metabolites, including a glutathione conjugate, are excreted renally. A single case report is published of intentional atrazine ingestion of 500 mL of a concentrate containing 100 g atrazine, 25 g amitrole, and 25 g ethylene glycol plus an uncharacterized amount of surfactant. The patient developed coma, shock, metabolic acidosis, gastrointestinal bleeding, renal failure, hepatic necrosis, and disseminated intravascular coagulation, and died on the third day. Much of this is compatible with surfactant toxicity except kidney and liver damage.

Management

Gastric decontamination may be indicated in any particular patient according to generally accepted principles (Chap. 8). Because liquid formulations are likely to be emulsifiable concentrates containing both surfactant and a hydrocarbon solvent, precautions must be taken to avoid both aspiration and esophageal trauma. There are no antidotes or specific treatment measures. Patients should be carefully monitored for adequate organ perfusion, respiratory effort, and oxygenation. Analysis of atrazine in biologic specimens is not routinely available.

112 Methyl Bromide and Other Fumigants

Fumigants are applied to control rodents, nematodes, insects, weed seeds, and fungi anywhere in the soil, structures, crop, grains, and commodities. Many different chemical classes have been used as fumigants, but only a few remain in use today in the United States. Most fumigants, especially many of the halogenated solvents, were abandoned because of their toxicity. While fumigants exist in all three physical states, they are most commonly used in the gaseous form, which explains why inhalation is the most common route of exposure.

METHYL BROMIDE

History and Epidemiology

Methyl bromide (CH_3Br) was used as an anesthetic in the early 1900s, but fatalities halted this practice. It was employed as a fire retardant during World War II, a role that persisted into the 1960s in Europe. Currently, its primary role is as a fumigant.

Methyl bromide and possibly other fumigants have also escaped from fumigated structures to adjacent or conjoined buildings, resulting in severe illness and fatalities. Underground pipes adjoining sections of a greenhouse have led to exposures. Fatalities have occurred when workers entered tanks containing fumigant residues. In Europe, indoor and outdoor exposures to old fire extinguishers have caused severe poisoning and fatalities.

Toxicokinetics

Dermal absorption of methyl bromide contributes to its toxicity. Significant individual variability exists for methyl bromide metabolism. Like methyl bromide, bioactivation followed by alkylation appear to be responsible for toxicity for the banned fumigant, ethylene bromide. The antifertility effects and toxicity of ethylene bromide are attributed to its alkylating, mustardlike, activity.

Pathology/Pathophysiology

Methyl bromide is highly neurotoxic. Autopsy findings demonstrate symmetric neuronal loss and gliosis in the inferior colliculi and the cerebellar dentate nuclei. These lesions are reportedly similar to those of the thiamine deficiency noted in Wernicke encephalopathy. The dorsal root ganglia also undergo neuronal loss. The peripheral nerves showed axonal and myelin loss with inflammatory changes. Methylation of the sulfhydryl groups of metabolic enzymes is proposed as a common mechanistic pathway.

Clinical Manifestations

Exposure to high concentrations of methyl bromide lead to immediate life-threatening toxicity, including a rapid loss of consciousness followed by seizures, dysrhythmias, and death. In contrast, symptoms may be delayed for days following low level exposure. Cardiopulmonary, hepatorenal, and neurologic manifestations may develop following methyl bromide exposure, as well as many of the other fumigants (Table 112–1).

TABLE 112–1. Comparison of Clinical Effects of Fumigants

Clinical Effect	Chloropicrin	Dichloropropene	Ethylene Dibromide	Metam Sodium	Methyl Bromide	Phosphine	Sulfuryl Fluoride
Mucus membrane irritation	+ +	+	+ +	+ +	± High concentration	+ +	± High concentration
Dermatitis		+	+	+	+		+
Burns (frostbite)	+			+	+		+
Gastrointestinal:							
Nausea, vomiting, abdominal pain	+	+	+	+	+	+	+
Hepatic dysfunction	+	+	+ +		+	+	
Chest pain	+	+	+			+	
Acute lung injury		+	+		+	+	+
Cardiovascular:							
Hypotension	+	+	+		+	+	+
Dysrhythmias		+	Late		+	+ +	+ +
Nephrotoxicity	+	+	+ +		+	+	
Mental status changes	+	+	+	+	+	+	+

+ = Presence; – = absence; ± = variable; ++ = very substantial.

Some individuals may initially manifest irritant symptoms of the eye, nasopharynx, and oropharynx, possibly related to chloropicrin, which is usually formulated as 2% of the methyl bromide concentration. The overlap of the irritant and nonspecific symptoms of methyl bromide and chloropicrin make it difficult to absolutely differentiate at the time of the exposure. In more severe poisoning cases, pulmonary symptoms may begin with cough or shortness of breath that may rapidly progress to bronchitis, pneumonitis, acute lung injury (ALI), and hemorrhage.

Initial central nervous system symptoms can include headache, vomiting, dizziness, drowsiness, euphoria, confusion, diplopia, dysmetria, dysarthria, and mood disorders or inappropriate affect. These may progress to ataxia, intention tremor, fasciculations, myoclonus, delirium, seizures, and coma.

Cutaneous lesions include erythema, vesicles, and bullae. Chronic exposure to methyl bromide is associated with hepatotoxicity and nephrotoxicity.

Diagnostic Testing

Although a serum bromide concentration does not facilitate the clinical management, an elevated concentration might help to confirm the diagnosis. Other standard laboratory tests should be obtained based on clinical needs. An elevated serum bromide concentration may cause a false elevation in serum chloride, when assayed using an ion selective electrode meter.

Treatment

Treatment for methyl bromide poisoning relies on general and supportive care. Decontamination should include the removal of clothing, as methyl bromide may bind to clothing, including rubber and leather. Irrigation of the eyes with saline and skin decontamination with soap and water should be performed. Because of the systemic toxicity of the halogenated fumigants, it is reasonable to administer at least one dose of oral activated charcoal following ingestion.

Seizures are common and difficult to control with traditional anticonvulsants such as benzodiazepines and phenytoin. Many cases have required pentobarbital coma and neuromuscular paralysis.

Prognosis

Most patients who develop seizures and coma will not survive. The few survivors of methyl bromide exposure described in the literature frequently have neuropsychiatric sequelae. Although improvement may occur over time, recovery is often incomplete.

DICHLOROPROPENE

Dichloropropene was introduced in 1945 and is primarily used as a soil fumigant for nematodes.

Occupational Exposure

Chronic subclinical changes have been reported in soil fumigators using dichloropropene in the Dutch flower bulb occupations. Various lymphomas are reported in firemen after dichloropropene exposure.

Toxicokinetics

The metabolism of dichloropropene likely resembles that of other chlorinated hydrocarbon solvents such as carbon tetrachloride and chloroform. The dose and route correlate with toxicity and outcome in rodent models. At 100 mg/kg in mice, hepatotoxicity occurs by the intraperitoneal route, but not after oral gavage. Hepatic failure and death was caused by intraperitoneal administration of 700 mg/kg. The inhalational route is the primary method of toxicity for dichloropropene. In a human volunteer study, dermal absorption of dichloropropene was only 2–5% of inhalational absorption.

Clinical Manifestations

There are a few reports of systemic dichloropropene toxicity. Tachycardia, tachypnea, hypotension, sweating, abdominal pain, and hematochezia occur rapidly after ingestion. Rhabdomyolysis, metabolic acidosis, hyperglycemia, and acute respiratory distress syndrome (ARDS) may also occur. Inhalation produces headache, neck pain, nausea, and dyspnea. Contact dermatitis may develop and healing leads to pigmented lesions.

Diagnostic Testing

Hepatic and renal function should be monitored following acute poisoning. No additional tests are recommended beyond those needed for supportive care.

Management

The patient's clothes should be removed and bagged to avoid continued inhalational and dermal exposure of the patient and the healthcare worker. If ingestion occurs, one dose of activated charcoal should be administered. There are no data to support specific therapies beyond supportive care.

PHOSPHIDES

Phosphides are usually found as powders or pellets, usually in the form of zinc or aluminum phosphide (Zn_3P_2 and AlP, respectively). Phosphine gas (PH_3) is formed from phosphides after contact with water, particularly if acidic. Phosphide tablets are often placed in grain stores, such as ships, allowing the phosphine to be released once the storage sites are sealed.

Many reports of serious phosphide poisoning, including fatalities, originate from India and other developing countries. The consumption of aluminum phosphide is a common choice for suicide in India. Clandestine methamphetamine laboratories that use the ephedrine–hydriodic acid–red phosphorus manufacturing method may generate phosphine gas at high reaction temperatures. Fatalities are reported, and first responders have also been exposed to high phosphine concentrations.

Toxicokinetics and Pathophysiology

Inhalation of phosphine gas results in nearly instant toxicity. Phosphides produce toxicity rapidly, generally within 30 minutes of ingestion, and death may follow in less than 6 hours. The ingestion of fresh, unopened tablets consistently results in toxicity, and ingestions larger than 500 mg are often fatal.

Phosphine disrupts mitochondrial function by blocking cytochrome-c oxidase. In addition to producing energy failure in cells, free radical generation increases resulting in lipid peroxidation.

Clinical Manifestations

Phosphides are potent gastric irritants; profuse vomiting and abdominal pain are often the first symptoms. Respiratory signs and symptoms include tachypnea, hyperpnea, dyspnea, cough, and chest tightness that may progress to acute lung injury over days. Tachycardia, hypotension and dysrhythmias may develop. Phosphine-induced dysrhythmias include atrial fibrillation and flutter, heart block, and ventricular tachycardia and fibrillation. Central nervous system toxicity includes coma, seizures, and delirium.

Diagnostic Testing

Phosphine tissue concentrations are not routinely available.

Management

Patients who ingest phosphine frequently vomit from the irritant effects of phosphine. Theoretically, off-gassing from emesis may expose healthcare workers to phosphine fumes. The emesis should be placed in sealed containers and disposed of properly, as wet phosphides will continue to generate phosphine gas. Vomiting makes activated charcoal administration difficult and raises the risk of aspiration. Because it is unknown to what extent activated charcoal binds phosphides and what the likely effectiveness of gastric evacuation by emesis is, administration of oral activated charcoal is probably unnecessary.

Comprehensive supportive care is recommended. Dilution with bicarbonate solution has been recommended, as bicarbonate is believed to decrease the gastric hydrochloric acid concentration which assists in the conversion of phosphides to phosphine gas.

SULFURYL FLUORIDE

History and Epidemiology

Sulfuryl fluoride is used as a structural fumigant insecticide, to control woodboring insects such as termites in homes. Structure or tent fumigation is performed by completely enclosing a house or other structure in plastic or a tarpaulin; the sulfuryl fluoride is pumped in as a compressed gas. Chloropicrin may be added as a warning agent.

Toxicokinetics and Pathophysiology

Little is known about the toxicokinetics of sulfuryl fluoride in humans. The mechanism of toxicity is not understood. The measurable fluoride concentrations in patients suggest that the release of fluoride may be a major pathophysiologic mechanism.

Clinical Manifestations

Case reports of sulfuryl fluoride exposure describe acute and subacute courses that have many similarities to methyl bromide. Initial symptoms may

be gastrointestinal, including nausea, vomiting, diarrhea, and abdominal pain, or respiratory, including cough and dyspnea. Irritation of mucosal surfaces may produce salivation, lacrimation with conjunctivitis, and nasopharyngitis. Severe exposures affect the cardiopulmonary and nervous systems.

Diagnostic Testing

Patients with sulfuryl fluoride exposure require frequent monitoring of serum calcium concentrations, as calcium complexes with fluoride ions (Chap. 101). Continuous cardiac monitoring should follow the QTc interval, as hypocalcemia may precipitate dysrhythmias. Serum fluoride concentrations, while not helpful for the acute management, may help with confirmatory diagnostic testing.

Management

After removal from the scene to fresh air, the patient should be disrobed to avoid the possibility of off-gassing of any sulfuryl fluoride gas. Aggressive treatment of hypocalcemia may be needed. Patients should have ECGs performed and be attached to continuous cardiac monitoring for QTc prolongation (Chap. 101). Similar to methyl bromide, supportive care may be needed for the seizures, dysrhythmias, and management of bronchospasm and ALI.

METAM SODIUM

Metam sodium, which breaks down into methyl isothiocyanate, is a potent sensitizer. It is among the more common causes of occupational exposure to fumigants. Exposed individuals develop irritant-induced asthma or reactive airways disease syndrome (RADS) and dermatitis.

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113 | Mushrooms

Because mushroom species vary widely with regard to the toxins they contain and identifying them with certainty is difficult, a clinical system of classification is more useful than a taxonomic system. In many cases, management and prognosis can be determined with a high degree of confidence from the history and initial symptoms. Ten groups of toxins are recognizable: cyclopeptides, gyromitrin, muscarine, coprine, ibotenic acid and muscimol, psilocybin, general gastrointestinal (GI) irritants, orellinine, allenic norleucine, and myotoxins. Table 113–1 is a general comparison of the mushroom poisoning syndromes.

GROUP I: CYCLOPEPTIDE-CONTAINING MUSHROOMS

Most mushroom fatalities are associated with the cyclopeptide-containing species. These mushrooms include a number of *Amanita* species, including *A. verna*, *A. virosa*, and *A. phalloides*, as well as *Galerina autumnalis*, *G. marginata*, *G. venenata*, *Lepiota helveola*, *L. josserandi*, and *L. brunneoincarnata*.

A. phalloides contains 15–20 cyclopeptides of which the amatoxins (cyclic octapeptides), phallotoxins (cyclic heptapeptides), and virotoxins (cyclic heptapeptides) are the best studied. Phalloidin, the principal phallotoxin, is a rapid-acting toxin, whereas amanitin tends to cause more delayed manifestations. Phalloidin interrupts actin polymerization and impairs cell membrane function, but because of its limited oral absorption, appears to have minimal toxicity, restricted mostly to GI dysfunction.

The amatoxins are the most toxic of the cyclopeptides, leading to hepatic, renal, and central nervous system (CNS) damage. α-Amanitin is the principal amatoxin responsible for human toxicity. Approximately 1.5–2.5 mg of amanitin can be obtained from 1 g of dry *A. phalloides*, and as much as 3.5 mg/g can be obtained from some *Lepiota* spp. A 20-g mushroom contains well in excess of the 0.1 mg/kg of amanitin considered lethal for humans. α-Amanitin interferes with RNA polymerase II, preventing the transcription of DNA. Target organs are those with the highest rate of cell turnover, including the gastrointestinal tract epithelium, hepatocytes, and kidneys. Pathologic manifestations include steatosis, central zonal necrosis, and centrilobular hemorrhage, with viable hepatocytes remaining at the rims of the larger triads. The amanitins are poorly, but rapidly absorbed from the GI tract, and α-amanitin is enterohepatically recirculated. Amatoxins show limited protein binding and are present in the plasma at low concentrations for 24–48 hours after ingestion.

Clinical Manifestations

Phase I of cyclopeptide poisoning resembles severe gastroenteritis, with profuse, watery diarrhea, not occurring until 5–24 hours after ingestion. Supportive fluid

TABLE 113–1. Mushroom Toxicity

Genus/Species	Toxin	Time of Onset of Symptoms	Primary Site of Toxicity	Symptoms	Mortality	Specific Therapy[a]
I.						
Amanita phalloides, A. tenuifolia, A. virosa *Galerina autumnalis, G. marginata, G. venenata* *Lepiota josserandi, L. helveola*	Cyclopeptides Amatoxins Phallotoxins	5–24 h	Hepatic	Phase I: GI toxicity-N V D Phase II: Quiescent, Phase III: Gastroenteritis, jaundice, AST, ALT	10–30%	Activated charcoal, Hemoperfusion, Penicillin G, Silibinin, NAL
II.						
Gyromitra ambigua, G. esculenta, G. infula	Gyromitrin (metabolite: monomethylhydrazine)	5–10 h	CNS	Seizures, abdominal pain, NV, weakness, hepatorenal failure	Rare	Benzodiazepines, Pyridoxine, 70 mg/kg IV
III.						
Clitocybe dealbata, Omphalotus olearius Most *Inocybe* spp	Muscarine	0.5–2 h	Autonomic nervous system	Muscarinic effects: salivation, bradycardia, lacrimation, urination, defecation, diaphoresis	Rare	Atropine: Adults: 1–2 mg Children: 0.02 mg/kg with a minimum of 0.1 mg
IV.						
Coprinus atramentarius	Coprine (metabolite: 1-aminocyclopropanol)	0.5–2 h	Aldehyde dehydrogenase	Disulfiramlike effect with ethanol, tachycardia, NV	Rare	—
V.						
Amanita gemmata, A. muscaria, A. pantherina	Ibotenic acid, muscimol	0.5–2 h	CNS	GABAergic effects, rare delirium, hallucinations, dizziness, ataxia	Rare	Benzodiazepines during excitatory phase

VI.						
Psilocybe caerulipes, P. cubensis *Gymnopilus spectabilis* *Psathyrella foenisecii*	Psilocybin, psilocin	0.5–1 h	CNS	Ataxia, NV, hyperkinesis, hallucinations	Rare	Benzodiazepines
VII.						
Clitocybe nebularis *Chlorophyllum molybdites, C. esculentum* *Lactarius* spp, *Paxillus involutus*	Various GI irritants	0.5–3 h	GI	Malaise, NVD	Rare	—
VIII.						
Cortinarius orellanus, C. speciosissimus, C. rainierensis	Orelline, orellanine	>24 h Days-weeks	Renal	Phase I: NV Phase II: Oliguria, renal failure	Rare	Hemodialysis for renal failure
IX.						
Amanita smithiana	Allenic norleucine	0.5–12 h	Renal	Phase I: NV Phase II: Oliguria, renal failure	None	Hemodialysis for renal failure
X.						
Tricholoma equestre	Unidentified myotoxin	24–72 h	Muscle (skeletal and cardiac)	Fatigue, N, muscle weakness, myalgias (↑CPK), facial erythema, diaphoresis, myocarditis	25%	—

D = diarrhea; N = nausea; V = vomiting.

[a]Supportive care (fluids, electrolytes, and antiemetics) as indicated.

Adapted, with permission, from Lincoff G, Mitchel DH: Toxic and Hallucinogenic Mushroom Poisoning: A Handbook for Physicians and Mushroom Hunters. New York, Van Nostrand Reinhold, 1977, pp. 246–247.

and electrolyte replacement leads to transient improvement during phase II, which occurs 12–36 hours after ingestion. However, despite such supportive care, phase III, manifested by hepatic and renal toxicity and death, may ensue 2–6 days after ingestion. Clinical hepatotoxicity with elevated bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), hypoglycemia, jaundice, and coma are not manifest until 2–3 days after the ingestion.

Management

The mainstay of therapy involves good supportive care with attention to fluid and electrolyte abnormalities. Multiple-dose activated charcoal (0.5–1 g/kg every 2–4 hours) is indicated based on its ability to adsorb toxin, demonstrated enterohepatic circulation, and improved survival in experimental models. Many antidotes have limited data to support their use. Penicillin G may have a time- and dose-dependent protective effect by either displacing α-amanitin from albumin, blocking its uptake from hepatocytes, binding circulating amatoxins, or preventing α-amanitin binding to RNA polymerase. Although the hepatoprotective effects of penicillin remain unclear, a dose of 1 million units of penicillin G/kg/d IV is recommended as safe and possibly efficacious. Silymarin is a lipophilic extract composed of three isomer flavonolignans; silibinin, silychristin, and silydianin. Silibinin, which represents approximately 50% of the extract but is 70–80% of the marketed product, inhibits hepatocellular penetration by α-amanitin. Although it is routinely available in health food stores and appears to be safe and well tolerated in patients with chronic liver disease, no reduction in mortality, improvement in histology at liver biopsy, or in biochemical markers has been defined. Despite this, silibinin is recommended for use in humans at a dose of 20–50 mg/kg/d, even though it is not FDA approved for use in the United States. NAL may also be useful, especially when hepatic failure is already present. Charcoal hemoperfusion should be considered for early presentations. Liver transplantation has been successful in the setting of fulminant hepatic failure.

GROUP II: GYROMITRIN-CONTAINING MUSHROOMS

Members of the gyromitrin group include *Gyromitra esculenta, G. californica, G. brunnea*, and *G. infula*. These mushrooms are found commonly in the spring under conifers, are easily recognized by their brainlike appearance, and are often confused with nongilled brainlike *Morchella esculenta* (morel).

Gyromitra mushrooms contain gyromitrin (*N*-methyl-*N*-formyl hydrazone), which splits into acetaldehyde and *N*-methyl-*N*-formyl hydrazine on hydrolysis. Subsequent hydrolysis, yields monomethylhydrazine. The hydrazine moiety reacts with pyridoxine (much like isoniazid), resulting in inhibition of pyridoxal phosphate-related enzymatic reactions. This interference with pyridoxal phosphate disrupts the function of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), leading to seizures.

Clinical Manifestations

The initial signs of toxicity occur 5–10 hours after ingestion and include nausea, vomiting, diarrhea, and abdominal pain. Patients complain of headaches, weakness, and diffuse muscle cramping. Most improve dramatically and return to normal within several days. Rarely, early in the clinical course, patients develop delirium, stupor, seizures, and coma. Infrequently, patients develop a hepatorenal syndrome.

Management

Under most circumstances supportive care is adequate. Activated charcoal (1 g/kg) should be given. Benzodiazepines are appropriate for the initial management of seizures. Pyridoxine in doses of 70 mg/kg IV may be useful for seizures that are refractory to benzodiazepines (see Antidotes in Brief: Pyridoxine).

GROUP III: MUSCARINE-CONTAINING MUSHROOMS

Mushrooms that contain muscarine include numerous members of the *Clitocybe* genus including *Clitocybe dealbata* (the sweater), *C. illudens (Omphalotus olearius)*, and the *Inocybe* genus, including *Inocybe iacera* and *I. geophylla*, among others. Muscarine and acetylcholine are similar structurally and have comparable clinical effects at the muscarinic receptors.

Clinical Manifestations

Symptoms begin within 30–120 minutes following ingestion. The peripheral manifestations typically include bradycardia, miosis, salivation, lacrimation, vomiting, diarrhea, bronchospasm, bronchorrhea, and micturition. Central muscarinic manifestations do not occur because muscarine, a quaternary ammonium compound, does not cross the blood–brain barrier. There are no nicotinic manifestations.

The effects of muscarine are often longer lasting than those of acetylcholine because of the lack of an ester bond, which makes muscarine resistant to hydrolysis by acetylcholinesterase.

Management

Significant toxicity is uncommon, limiting the need for more than supportive care. Rarely, atropine (1–2 mg given IV slowly for adults or 0.02 mg/kg with a minimum of 0.1 mg IV for children) can be titrated and repeated as frequently as indicated to reverse severe toxicity.

GROUP IV: COPRINE-CONTAINING MUSHROOMS

Coprinus mushrooms, particularly *Coprinus atramentarius*, contain the toxin coprine. These mushrooms grow abundantly in temperate climates in grassy and woodland fields. They are known as "inky caps" because the gills that contain a peptidase autodigest into an inky liquid shortly after picking. Coprine, an amino acid, its primary metabolite 1-aminocyclopropanol, or more likely a secondary in vivo hydrolytic metabolite, cyclopropanone hydrate, inhibits aldehyde dehydrogenase. This results in the buildup of acetaldehyde with its accompanying adverse effects, which occur if the patient ingests alcohol concomitantly or for as long as 48–72 hours after the mushroom ingestion.

Clinical Manifestations

Within 0.5–2 hours of ethanol ingestion, patients develop tachycardia, flushing, nausea, and vomiting characteristic of a disulfiram reaction. The clinical manifestations are usually mild and resolve within several hours.

Management

Treatment is symptomatic with fluid repletion and antiemetics as needed.

GROUP V: IBOTENIC ACID- AND MUSCIMOL-CONTAINING MUSHROOMS

Most of the mushrooms in this class are primarily in the *Amanita* genus, which includes *Amanita muscaria* (fly agaric), *A. pantherina*, and *A. gemmata*. They exist singly and are scattered throughout the US woodlands. The brilliant red or tan cap is that of the mushroom commonly depicted in children's books, and is easily recognized in the fields during summer and fall.

Small quantities of the isoxazole derivatives ibotenic acid and muscimol are found in these mushrooms, which have been used throughout history in religious customs. Ibotenic acid is structurally similar to the stimulatory neurotransmitter glutamic acid. The stereochemistry of muscimol is very similar to that of the neurotransmitter GABA.

Clinical Manifestations

Most patients who develop symptoms have intentionally ingested large quantities of these mushrooms seeking an hallucinatory experience. Within 0.5–2 hours of ingestion, these compounds produce the GABAergic manifestations of somnolence, dizziness, hallucinations, dysphoria, and delirium in adults, whereas the excitatory glutamatergic manifestations of myoclonic movements, seizures, and other neurologic findings predominate in children.

Management

Most symptoms respond solely to supportive care, although benzodiazepines are appropriate for any of the excitatory central nervous system manifestations.

GROUP VI: PSILOCYBIN-CONTAINING MUSHROOMS

Psilocybin-containing mushrooms include *Psilocybe caerulescens, P. cubensis, Conocybe cyanopus, Panaeolus foenisecii, Gymnopilus spectabilis*, and *Psathyrella foenisecii*. Toxicity from this group is very common because of the popularity of hallucinogens. Psilocybin is rapidly and completely hydrolyzed to psilocin in vivo. Serotonin, psilocin, and psilocybin are very similar structurally and presumably act at the 5-HT_2 receptor.

Clinical Manifestations

Within 1 hour of ingestion CNS effects, including ataxia, hyperkinesis, visual illusions, and hallucinations, may begin, peaking by 4 hours. Some patients develop anxiety, tachycardia, tremor, agitation, and may have mydriasis. Patients typically return to normal within 6–12 hours.

Management

Treatment for the hallucinations is usually supportive, although benzodiazepines may be necessary when reassurance proves inadequate.

GROUP VII: GASTROINTESTINAL TOXIN-CONTAINING MUSHROOMS

By far the largest group of mushrooms is a diverse group that contains a variety of ill-defined GI toxins. Many of the hundreds of mushrooms in this group fall into the "little brown mushroom" category. Some *Boletus*, *Lactarius* spp, *O. olearius, Rhodophyllus* spp, *Tricholoma* spp, *Chlorophyllum mo-*

lybdites, and *C. esculentum* are mistaken for edible or hallucinogenic species. The specific toxins associated with this group have not been identified.

Clinical Manifestations

Gastrointestinal toxicity occurs 0.5–3 hours after ingestion when epigastric distress, malaise, nausea, vomiting, and diarrhea are evident.

Management

Treatment is supportive and it involves fluid resuscitation, and antiemetics as needed. The clinical course is brief and the prognosis excellent.

GROUP VIII: ORELLANINE- AND ORELLINE-CONTAINING MUSHROOMS

Cortinarius mushrooms, such as *Cortinarius speciosissimus* and *C. orellanus*, are commonly found throughout Europe and *C. rainierensis* is a common North American species. The toxic compound orellanine is a hydroxylated bipyridine compound activated by its metabolism through the cytochrome P450 system. Toxicologically, it is similar to paraquat and diquat, and may have comparable mechanisms of action, although precise knowledge is limited.

Clinical Manifestations

The initial symptoms occur 24–36 hours after ingestion and include headache, chills, polydipsia, anorexia, nausea, vomiting, and flank and abdominal pain. Several days to weeks later, oliguric renal failure may develop. The only initial laboratory abnormalities may be hematuria, leukocyturia, and proteinuria. Nephrotoxicity is characterized by interstitial nephritis with tubular damage and early fibrosis of injured tubules with relative glomerular sparing.

Management

Treatment is entirely supportive, with hemodialysis only indicated for critical renal dysfunction. Many patients will recover, although varying degrees of renal dysfunction may persist.

GROUP IX: ALLENIC NORLEUCINE-CONTAINING MUSHROOMS

This relatively new diagnostic group is currently only associated with the ingestion of *A. smithiana*. It appears that all of the poisoned individuals were seeking the edible pine mushroom matsutake (*Tricholoma magnivelare*), a highly desirable look-alike. These mushrooms possess two toxins: allenic norleucine (aminohexadienoic acid) and L-2-amino-4-pentynoic acid. Renal epithelial tissue cultured in vitro with allenic norleucine developed morphologic changes similar to those described in patients who ingested *A. smithiana*.

Clinical Manifestations

Symptoms develop from 30 minutes to 12 hours following ingestion. Gastrointestinal manifestations, including anorexia, nausea, vomiting, abdominal distress, and diarrhea, are accompanied by malaise, sweating, and dizziness. Acute renal failure manifests 4–6 days following ingestion with marked elevation of BUN and creatinine.

Management

There is no known antidote for these nephrotoxins. Activated charcoal, although of no proven benefit, should be used when a patient in the American northwest presents with early gastrointestinal manifestations. Hemodialysis is indicated when renal dysfunction becomes severe. Although several patients did not require hemodialysis, those who did were dialyzed 2–3 times per week for approximately 1 month.

GROUP X: RHABDOMYOLYSIS-ASSOCIATED MUSHROOMS

Twelve patients who ingested *T. equestre (T. flavovirens)* mushrooms for three consecutive days developed severe rhabdomyolysis that was lethal in three cases. All patients developed fatigue, muscle weakness, and myalgia 24–72 hours following the last mushroom meal. The mean maximal creatine phosphokinase (CPK) was 226,067 U/L in women and 34,786 U/L in men, with some values greater than 500,000 U/L. Electromyography revealed muscle injury with myotoxic activity. In the three patients, dyspnea, muscle weakness, pulmonary congestion, acute myocarditis, dysrhythmias, cardiac failure, and death ensued. Autopsy demonstrated myocardial lesions identical to those found in the peripheral muscles.

Management

There is no antidote. Supportive care should focus on maintaining urine output to prevent myoglobinuric renal failure. Hemodialysis may be required.

GENERAL APPROACH TO INGESTION OF AN UNKNOWN MUSHROOM

The clinical details provided above are sufficient to evaluate most cases. When a patient with a characteristic toxidrome presents early, diagnosis and management can proceed accordingly. Patients whose symptoms begin beyond 4–6 hours after ingestion should be presumed to have ingested an amatoxin-, gyromitrin-, or orellanine-containing mushroom, necessitating decontamination, admission, close observation, and the potential use of antidotes. Although these principles may be violated by mushrooms containing allenic norleucine, such cases are rare and geographically restricted. Confusion may exist when multiple types of mushrooms have been ingested and GI symptoms begin early and persist beyond 4–6 hours after ingestion. Those patients should be presumed to have ingested mushrooms with delayed toxicity.

114 Plants

EPIDEMIOLOGY

Exposures to plants are among the most common calls to poison centers in the United States, accounting for 5–10% of all calls. The vast majority (85%) of calls occur in children younger than age 6 years and are unintentional ingestions. Approximately 3% involve skin or eye exposure. The most common plant calls are listed in Table 114–1 and are nontoxic or result only in mild GI symptoms. It should be noted that in contrast to household exposures, most occupational exposures are cutaneous and go unreported.

Death or significant illness from unintentional exposure is so rare that it is essentially unreported. In contrast, intentional exposure in the setting of confusion for foodstuff's, herbal remedies or attempted abuse can easily produce life-threatening toxicity. Table 114–2 lists the plants most likely to cause serious toxicity in humans. The issue of herbal medicine overlaps dramatically with plant toxicity and is discussed in Chap. 43. Certain plant toxins are discussed extensively in other sections: Chaps. 37, 63, 80–82, 108, and 127, and Antidotes in Brief: Syrup of Ipecac.

IDENTIFICATION OF PLANTS

Positive identification of the plant species should be attempted whenever possible, especially when the patient becomes symptomatic. Communication with an expert botanist or poison center is highly recommended and can be facilitated by transmission of digital images or a facsimile (fax). Simple comparison of the species in question with pictures or descriptions from a field guide or flora may help to confirm or exclude the identity. This can be done in part from cross-referencing information in Tables 114–3 and 114–4 with the clinical symptoms discussed below. A plant identification also can be compared with those searched in the PLANTOX database (http://vm.cfsan.fda.gov/~djw/readme.html), which is managed by the Food and Drug Administration. Laboratory analysis is not timely enough to be useful except as a tool in an investigatory or forensic analysis.

CLASSIFICATION OF PLANT TOXICITY

When the plant is definitively identified, Tables 114–3 and 114–4 serve as resources to determine the most likely symptoms. It should be noted however, that plant chemistry is complex and Table 114–4 presents a simplified presentation of one toxin class/symptom group per plant.

When the plant is not available or cannot be identified, clinical signs and symptoms can help guide both the identification and the management. Often, the precise identification is not required to properly care for the patient.

CLINICAL SYNDROMES OF PLANT EXPOSURE

Anticholinergic Effects: Belladonna Alkaloids

The belladonna alkaloids are all from the family Solanaceae and have potent antimuscarinic effects. Ingestion produces classic signs of: tachycardia, hypertension,

TABLE 114–1. Most Common Plants Involved in Calls to US Poison Centers

Common Name	Botanical Name
Devil's ivy	*Epipremnum aureum*
Dumbcane	*Dieffenbachia* spp
Holly	*Ilex* spp
Jade plant	*Crassula* spp
Peace lily	*Spathiphyllum* spp
Pepper (chili)	*Capsicum annuum*
Philodendron	*Philodendron* spp
Poinsettia	*Euphorbia pulcherrima*
Poison ivy/poison oak	*Toxicodendron* spp
Pokeweed	*Phytolacca americana*

hyperthermia, dry skin and mucous membranes, skin flushing, diminished bowel sounds, urinary retention, agitation, disorientation, and hallucinations (Chap. 50). Hallucinatory effects are sought in seeds and teas made from jimsonweed (*Datura stramonium*). One hundred of these seeds contain up to 6 mg of atropine and related alkaloids and such an ingestion can be fatal. Table 114–5 describes various anticholinergic plants. Treatment is identical to other anticholinergic poisoning (Chap. 50 and Antidotes in Brief: Physostigmine Salicylate).

Solanaceous Alkaloids

Solanine is contained in other members of the Solanaceae family but it is not a belladonna alkaloid; however, most symptomatic patients more typically develop nausea, vomiting, diarrhea, and abdominal pain that begin 2–24 hours after ingestion, and may persist for several days. Green potatoes and green potato tops are most commonly associated with symptoms, which is not surprising, because that is where the alkaloids are most concentrated.

Nicotine and Nicotinelike Alkaloids: Nicotine, Lobeline, Sparteine, *N*-Methylcytisine, Cytisine, and Coniine

Nicotine toxicity occurs via ingestion of leaves of *Nicotiana tabacum*, cigarette remains, organic insecticides, and transdermally among farm workers harvesting tobacco (green tobacco sickness). A dose considered lethal to an adult may be as little as 1 mg/kg. Overstimulation of the nicotinic receptors by high doses of nicotine produces gastrointestinal symptoms, diaphoresis, mydriasis, fasciculations, tachycardia, hypertension, hyperthermia, seizures, respiratory depression, and death (Chap. 82). Many other alkaloids, lobeline, sparteine, *n*-methylcytisine, cytisine, and coniine (poison hemlock) produce similar toxicity.

TABLE 114–2. Plants Most Likely to Cause Serious Toxicity

Common Name	Botanical Name
Jequirity pea	*Abrus precatorius*
Jimsonweed	*Datura stramonium*
Monkshood	*Aconitum napellus*
Oleander	*Nerium oleander*
Poison hemlock	*Conium maculata*
Water hemlock	*Cicuta maculata*

TABLE 114–3. Nontoxic Houseplants[a]

Common Name	Botanical Name
African violet	*Saintpaulia ionantha* or *Episcia reptans*
Aluminum plant	*Pilea cadierei*
Aralia, false	*Dizygotheca elegantissima* or *Fatsia japonica*
Baby's tears	*Helxine soleirolii*
Begonia	*Begonia semperflorens*
Bird's nest fern	*Asplenium nidus*
Boston fern	*Nephrolepsis exalta*
Bridal veil	*Tradescantia*
Christmas cactus	*Schlumberga bridgesii*
Coleus	*Coleus blumei*
Corn plant	*Dracena fragrans*
Creeping Charlie	*Pilea nummularifolia, Plectranthus australis*
Creeping Jenny	*Lysimachia nummularia*
Donkey tail	*Sedum morganianun*
Emerald ripple	*Peperomia caperata*
Fiddleleaf fig	*Ficus lyrata*
Gardenia	*Gardenia radicans*
Grape ivy	*Cissus rhombifolia*
Hawaiian ti	*Cordyline terminalis*
Hen and chicks	*Echeveria* spp, *Sempervivum tectorus*
Jade tree	*Crassula argentea*
Lipstick plant	*Aeschyanthus lobbianus*
Monkey plant	*Ruellia makoyana*
Mother-in-law's tongue	*Sansevieria trifasciata*
Parlor palm	*Chamaedorea elegans*
Peacock plant	*Calathea makoyana*
Piggy-back plant	*Tolmiea menziesii*
Pink polka dot plant	*Hypoestes phyllostachya*
Prayer plant	*Maranta leuconeura*
Rosary vine[b]	*Ceropegia woodii*
Rosary pearls[b]	*Senico rowleyanus* or *Senico herreianus*
Rubber plant	*Ficus elastica*
Sensitive plant	*Mimosa pudica*
Snake plant	*Sansevieria trifasciata*
Spider plant	*Chlorophytum comosum*
String of hearts	*Creopegia woodii*
Swedish ivy	*Plectranthus australis*
Umbrella plant (Schefflera)	*Brassaia actinophylla*
Wandering Jew	*Tradescantia albiflora, Zebrina pendula*
Wax plant	*Hoya camosa* or *Hoya exotica*
Weeping fig	*Ficus benjamina*
Zebra plant	*Aphelandra squarrosa*

It should be noted that several different species have identical common names.
[a]Some may cause diarrhea in infants.
[b]Should not be confused with the toxic rosary pea (*Abrus precatorius*).

Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids are widely distributed both botanically and geographically, and are found in 6000 plants and in 13 plant families, but are most heavily represented within the Boraginaceae, Compositae, and Fabaceae.

TABLE 114–4. Primary Toxicity of Common Important Plant Species

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Abrus precatorius (Euphorbiaceae)[a]	Prayer beans, rosary pea, Indian bean, crab's eye, Buddhist's rosary bead, prayer bead, jequirity pea	Gastrointestinal	Abrin	Protein, lectin, peptide, amino acid
Aconitum napellus and other *Aconitum* spp (Ranunculaceae)[a]	Monkshood and others	Cardiac, neurologic	Aconitine and related compounds	Alkaloid
Acorus calamus (*Araliaceae*)	Sweet flag, rat root, flag root, calamus	Gastrointestinal	Asarin	Phenol or phenylpropanoid
Aesculus hippocastanum (Hippocastanaceae)	Horse chestnut	Hematologic	Esculoside (6-β-D-glucopyranosyloxy-7-hydroxycoumarin)	Phenol or phenylpropanoid
Agave lecheguilla (Amaryllidaceae)	Agave	Dermatitis: hematogenous photosensitivity in animals	Steroidal saponins (aglycones: smilagenin, sarsasapogenin)	Saponin glycoside
Aloe barbadensis, A. vera, others (Liliaceae/Amaryllidaceae)	Aloe	Gastrointestinal	Barbaloin, iso-barbaloin, aloinosides	Anthraquinone glycoside
Anabaena and *Aphanizomenon*[a]	Blue green algae	Neurologic	Saxitoxin equivalents	Guanidinium compound
Anacardium occidentale, many others (Anacardaceae)	Cashew, many others	Dermatitis: contact, allergic	Urushiol oleoresins	Terpenoid
Anthoxanthum odoratum (Poaceae)	Sweet vernal grass	Hematologic	Coumarin	Phenol or phenylpropanoid
Areca catechu (Aracaceae)	Betel	Cholinergic	Arecoline	Alkaloid
Argemone mexicana (Papaveraceae)	Mexican pricklepoppy	Gastrointestinal	Sanguinarine	Alkaloid
Argyreia nervosa	Hawaiian baby woodrose seeds	Neurologic	Lyserg acid amide, lyserg acid ethylamide	Alkaloid
Argyreia spp (Convolvulaceae)	Morning glory	Neurologic	Lysergic acid derivatives	Alkaloid

Aristolochia reticulata, A. spp (Aristolochiaceae)[a]	Texan or Red River snake root, numerous	Renal, carcinogenic	Aristolochic acid	Alkaloid relative as derivative of isothebaine
Artemisia absinthium (Compositaceae/Asteraceae)[a]	Absinthe	Neurologic	Thujone	Terpenoid
Asclepias spp (Asclepidaceae)[a]	Milk weed	Cardiac	Asclepin and related cardenolides	Cardioactive steroid
Astragalus spp (Fabiaceae)[a]	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
Atractylis gummifera (Compositaceae)[a]	Thistle	Hepatic	Atractyloside, gummiferine	Glycoside
Atropa belladonna (Solanaceae)[a]	Belladonna	Anticholinergic	Belladonna alkaloids	Alkaloid
Azalea spp (Ericaceae)[a,b]	Azalea	Cardiac, neurologic	Grayanotoxin	Terpenoid
Berberis spp (Ranunculaceae)	Barberry	Oxytocic, cardiovascular	Berberine	Alkaloid
Blighia sapida (*Sapindaceae*)[a]	Ackee fruit	Metabolic, gastrointestinal, neurotoxic	Hypoglycin	Protein, lectin, peptide, amino acid
Borago officinalis (Boragniaceae)[a]	Borage	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Brassaia spp[b]	Umbrella tree	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Brassica nigra (Brassicaceae)	Black mustard	Dermatitis: irritant	Sinigrin	Glucosinolate (isothiocyanate glycoside)
Brassica olearacea var. *capitata*	Cabbage	Metabolic (precursor to goitrin, antithyroid compound)	Progoitrin	Isothiocyanate glycoside
Cactus spp[b]	Cactus	Dermatitis: mechanical	Nontoxic	None
Caladium spp (Araceae)[b]	Caladium	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Calotropis spp (Asclepidaceae)[a]	Crown flower	Cardiac	Asclepin and related cardenolides	Cardioactive steroid
Camellia sinensis (Theaceae)	Tea, green tea	Cardiac, neurologic	Theophylline, caffeine	Alkaloid

(continued)

TABLE 114–4. Primary Toxicity of Common Important Plant Species *(continued)*

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Cannibis sativa	Cannibis, marijuana, Indian hemp, hashish, pot	Neurologic	Tetrahydrocannabinol	Terpenoid, resin, oleoresin
Capsicum frutescens, C. annuum, C. spp (Solanaceae)[b]	Capsicum, cayenne pepper	Dermatitis: irritant	Capsaicin	Phenol or phenylpropanoid
Cascara sagrada = Rhamnus purshiana = R. cathartica (Rhamnaceae)	Cascara, sacred bark, Chittern bark, common buckthorn	Gastrointestinal	Cascarosides, *O*-glycosides, emodin	Anthraquinone glycoside
Cassia senna, *C. angustifolia* (Fabaceae)	Senna	Gastrointestinal	Sennosides	Anthraquinone glycoside
Catha edulis (Celastaceae)	Khat	Cardiac, neurologic	Cathinone	Alkaloid
Catharanthus roseus (formerly *Vinca rosea*) (Apocynaceae)	Catharanthus, vinca, Madagascar periwinkle	Gastrointestinal	Vincristine	Alkaloid
Caulophyllum thalictroides (Berberidaceae)	Blue cohosh	Nicotinic	*N*-Methylcytisine and related compounds	Alkaloid
Cephaelis ipecacuanha, C. acuminata (Rubiaceae)[a]	Ipecac	Gastrointestinal, cardiac	Emetine/cephaline	Alkaloid
Chlorophytum comosum[b]	Spider plant	Dermatitis: contact, allergic	Urushiol oleoresins	Terpenoid
Chondrodendron spp, *Curarea* spp, *Strychnos* spp[a]	Tubocurare, curare	Neurologic	Tubocurarine	Alkaloid
Chrysanthemum spp, *Taraxacum officinale,* many other Compositaceae (Asteraceae)[b]	Chrysanthemum, dandelion, other Compositaceae	Dermatitis: contact, allergic	Sesquiterpene lactones	Terpenoid
Cicuta maculata (Apiaceae/Umbelliferae)[a]	Water hemlock	Neurologic	Cicutoxin	Alcohol
Cinchona spp (Rubiaceae)[a]	Cinchona	Cardiac, cinchonism	Quinidine	Alkaloid
Citrus aurantium (Rutaceae)[a]	Bitter orange	Cardiac, neurologic	Synephrine	Alkaloid
Citrus paradisi (Rutaceae)	Grapefruit	Hepatic drug interactions	Bergamottin, naringenin, or naringen	Phenol or phenylpropanoid

Claviceps purpurea, C. paspali (Claviceptacea = fungus)[a]	Ergot	Cardiac, neurologic, oxytocic	Ergotamine and related compounds	Alkaloid
Coffea arabica (Rubiaceae)	Coffee	Cardiac, neurologic	Caffeine	Alkaloid
Cola nitida, Cola spp (Sterculiaceae)	Kola nut	Cardiac, neurologic	Caffeine	Alkaloid
Colchicum autumnale (Liliaceae)[a]	Autumn crocus	Multisystem	Colchicine	Alkaloid
Conium maculatum (Apiaceae/Umbelliferae)[a]	Poison hemlock	Nicotinic, neurologic, respiratory, renal	Coniine	Alkaloid
Convallaria majalis[a]	Lily of the valley	Cardiac	Convallatoxin, strophanthin (~40 others)	Cardioactive steroid
Coptis spp (Ranunculaceae)	Goldenthread	Oxytocic, cardiovascular	Berberine	Alkaloid
Crassula spp[b]	Jade plant	Gastrointestinal	Nontoxic	None
Crotalaria spp (Fabaceae)[a]	Rattlebox	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Croton tiglium and C. spp (Euphorbiaceae)	Croton	Carcinogen, gastrointestinal	Croton oil	Lipid and fixed oil, also contains tropane alkaloid and diterpene
Cycas circinalis[a]	Queen sago, indu, cycad	Neurologic	Cyacasin	Glycosides
Cytisus scoparius (Fabaceae)[a]	Broom, Scotch broom	Nicotinic, oxytocic	Sparteine	Alkaloid
Datura stramonium (Solanaceae)[a]	Jimson weed, stramonium, locoweed	Anticholinergic	Belladonna alkaloids	Alkaloid
Delphinium spp (Ranunculaceae)[a]	Larkspur, others	Cardiac, neurologic	Methyllycaconitine and related compounds	Alkaloid
Dieffenbachia spp (Araceae)[b]	Dieffenbachia	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Digitalis lanata[a]	Grecian foxglove	Cardiac	Digoxin, Lanatosides A-E (contains ~70 cardioactive steroids)	Cardioactive steroid

(continued)

TABLE 114–4. Primary Toxicity of Common Important Plant Species *(continued)*

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Digitalis purpurea[a]	Purple foxglove	Cardiac	Digitoxin	Cardioactive steroid
Dipteryx odorata, D. oppositifolia (Fabaceae/Legumaceae)	Tonka beans	Hematologic	Coumarin	Phenol or phenylpropanoid
Ephedra spp, especially *sinensis* (Ephedraceae/Gnetaceae = Gymnosperm)[a]	Ephedra, Ma-huang	Cardiac, neurologic	Ephedrine and related compounds	Alkaloid
Epipremnum aureum (Araceae)[b]	Pothos ivy	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Erythroxylum coca	Coca	Neurologic, cardiac	Cocaine	Alkaloid
Eucalyptus globus or spp[b]	Eucalyptus	Dermatitis: contact, allergic	Eucalyptol	Terpenoid
Euphorbia pulcherrima, E. spp (Eurphorbiaceae)[b]	Poinsettia	Dermatitis: contact, allergic	Phorbol esters	Terpenoid
Ficus benjamina[b]	Weeping fig tree	Nontoxic	Nontoxic	None
Galium triflorum (Rubiaceae)	Sweet-scented bedstraw	Hematologic	Coumarin	Phenol or phenylpropanoid
Ginkgo biloba (Ginkgoaceae)[a]	Ginkgo	Dermatitis: contact, allergic Hematologic, neurologic	Urushiol oleoresins Ginkgolides A–C, M 4-Methoxypyridoxine in seeds only	Terpenoid,alkaloid, pyridine
Gloriosa superba (Liliaceae)[a]	Meadow saffron	Multisystem	Colchicine	Alkaloid
Glycyrrhiza glabra[a]	Licorice	Metabolic, renal	Glycyrrhizin	Saponin glycoside
Gossypium spp	Cotton, cottonseed oil	Metabolic	Gossypol	Terpenoid
Hedeoma pulegioides (Lamiaceae)[a]	Pennyroyal	Hepatic, neurologic, oxytoxic	Pulegone	Terpenoid
Hedera helix (Araliaceae)[b]	Common ivy	Not absorbed	Hederacoside C, α-hederin, hederagenin	Cardioactive steroid
Hedysarium alpinum (Fabiaceae)	Wild potato	Metabolic, neurologic	Swainsonine	Alkaloid

Heliotropium spp (Compositae/Asteraceae)[a]	Ragwort	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Helleborus niger[a]	Black hellebore, Christmas rose	Cardiac	Hellebrin	Cardioactive steroid
Hydrastis canadensis (Ranunculaceae)[a]	Goldenseal	Neurologic, oxytocic, cardiovascular, respiratory	Hydrastine, berberine	Alkaloid
Hyoscyamus niger (Solanaceae)[a]	Henbane, hyoscyamus	Anticholinergic	Belladonna alkaloids	Alkaloid
Hypericum perforatum (Clusiaceae)	St. John's wort	Dermatitis: photosensitivity, neurologic, hepatic microsomal drug interactions	Hyperforin or other	Terpenoid
Ilex paraguariensis (Aquifoliaceae)	Maté, Yerba Maté, Paraguay tea	Cardiac, neurologic	Caffeine	Alkaloid
Ilex spp berries (Aquifoliaceae)[b]	Holly	Gastrointestinal	Mixture: Alkaloids, polyphenols, saponins, steroids, triterpenoids	Unidentified
Illicium anasatum (Illiciaceae)[a]	Japanese Star anise	Neurologic	Anasatin	Terpenoid
Ipomoea tricolor and other *Ipomoea* spp (Convolvulaceae)	Morning glory	Neurologic	Lysergic acid derivatives	Alkaloid
Jatropha curcas (Euphorbiaceae)	Black vomit nut, physic nut, purging nut	Gastrointestinal	Curcin	Lectin
Karwinskia humboldtiana[a]	Buckthorn, wild cherry, tullidora, coyatillo, capulincillo, others	Neurologic, respiratory	Toxin T-454, others	Phenol or phenylpropanoid
Laburnum anagyroides (syn. *Cytisus laburnum*; Fabaceae)[a]	Golden chain, laburnum	Nicotinic	Cytisine	Alkaloid
Lantana camara (Verbenaceae)	Lantana	Dermatitis: hepatogenous photosensitivity	Lantadene A and B, phylloerythrin	Terpenoid

(continued)

TABLE 114–4. Primary Toxicity of Common Important Plant Species *(continued)*

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Lathyrus sativus[a]	Grass pea	Neurologic, skeletal	β-*N*-oxalylamino-L-alanine (BOAA); β-aminopropionitrile (BAPN)	Amino acid
Lobelia inflata (Campanulaceae)	Indian tobacco	Nicotinic	Lobeline	Alkaloid
Lophophora williamsii	Peyote or mescal buttons	Neurologic	Mescaline	Alkaloid
Lupinus latifolius and other *Lupinus* spp (Fabaceae)	Lupin	Nicotinic	Anagyrine	Alkaloid
Lycopersicon spp (Solanaceae)[a]	Tomato (green)	Gastrointestinal, neurologic, some anticholinergic	Solanine, chaconine	Alkaloid
Mahonia spp (Ranunculaceae)	Oregon grape	Oxytocic, cardiovascular	Berberine	Alkaloid
Mandragora officinarum (Solanaceae)[a]	European or true mandrake	Anticholinergic	Belladonna alkaloids	Alkaloid
Manihot esculenta (Euphorbiaceae)[a]	Cassava, manihot, tapioca	Metabolic, neurotoxic: motor spastic paresis and vision disturbance with chronic use	Linamarin	Cyanogenic glycoside
Melilotus spp (Fabaceae/Legumaceae)	Sweet clover	Hematologic	Coumarin	Phenol or phenylpropanoid
Mentha pulegium (Lamiaceae)[a]	Pennyroyal	Hepatic, neurologic, oxytoxic	Pulegone	Terpenoid
Microcystis and *Anabaena* spp	Blue-green algae (planktonic cyanobacteria)	Hepatotoxic, dermatitis: photosensitivity	Microcystin	Lectin
Myristica fragrans	Nutmeg, pericarp = mace	Neurologic (hallucinations with 15 g)	Myristicin, elemicin	Terpenoid
Narcissus spp and other (Amaryllidaceae, Liliaceae)	Narcissus	Dermatitis: mechanical and cytotoxic	Lycorine, homolycorin	Alkaloid
Nerium oleander[a]	Oleander	Cardiac	Oleandrin	Cardioactive steroid

Nicotiana tabacum and other *Nicotiana* spp (Solanaceae)[a]	Tobacco	Nicotinic	Nicotine	Alkaloid
Oxytropis spp (Fabiaceae)	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
Papaver somniferum	Poppy with opium derivatives	Neurologic	Morphine/other opium derivatives	Alkaloid
Paullinia cupana (Sapindaceae)	Guarana	Cardiac, neurologic	Caffeine	Alkaloid
Pausinystalia yohimbe (Rubiaceae)[a]	Yohimbe	Cardiac, cholinergic	Yohimbine	Alkaloid
Philodendron spp (Araceae)[b]	Philodendron	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Phoradendron spp (Loranthaceae or Viscaceae)	American mistletoe	Gastrointestinal	Phoratoxin, ligatoxin	Lectin
Physostigma venenosum (Fabaceae)[a]	Calabar bean, ordeal bean	Cholinergic	Physostigmine	Alkaloid
Phytolacca americana (Phytolaccaceae)[a]	Pokeweed, Indian poke, poke, inkberry, scoke, pigeonberry, garget, American cancer	Gastrointestinal	Phytolaccatoxin	Lectin
Pilocarpus jaborandi, P. pinnatifolius (Rutaceae)[a]	Pilocarpus, jaborandi	Cholinergic effects (muscarinic)	Pilocarpine	Alkaloid
Piper methysticum[a]	Kava kava	Hepatic, neurologic	Kawain, methysticine yangonin, other kava lactones	Terpenoid, resin, and oleoresin
Plantago spp seed husks (Plantaginaceae)	Plantago	Gastrointestinal	Psyllium	Carbohydrate
Podophyllum emodi and *Podophyllum peltatum* (Berberidaceae)[a]	Wild mandrake, mayapple	Multisystem	Podophyllin (lignan)	Phenol or phenylpropanoid

(continued)

TABLE 114–4. Primary Toxicity of Common Important Plant Species *(continued)*

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Populus spp (Salicaceae)	Poplar species	Cinchonism	Salicin	Glycoside
Primula obconica (Primulaceae)	Primrose	Dermatitis: contact, allergic	Primin	Phenol or phenylpropanoid
Prunus armeniaca, *Prunus* spp, *Malus* spp (Rosaceae)[a]	Apricot seed pits, wild cherry, peach, plum, pear, almond, apple and other seed kernels	Metabolic acidosis, respiratory failure, coma, death	Amygdalin, emulsin	Cyanogenic glycoside
Pteridum spp (Polypodiaceae)	Brachen fern	Carcinogen, thiaminase	Ptaquiloside	Terpenoid
Pulsatilla spp (Ranunculaceae)	Pulsatilla	Dermatitis: contact	Ranunculin, protoanemonin	Glycoside
Quercus spp	Oak	Metabolic: oak toxicosis in livestock	Tannic acid	Phenol or phenylpropanoid
Ranunculus spp (Ranunculaceae)	Pilewort and other buttercups	Dermatitis: contact	Ranunculin, protoanemonin	Glycoside
Rauwolfia serpentina (Apocynaceae)	Indian snakeroot	Cardiac, neurologic	Reserpine	Alkaloid
Remijia pedunculata (Rubiaceae)[a]	Cuprea bark	Cardiac, cinchonism	Quinidine	Alkaloid
Rhamnus frangula (Rhamnaceae)	Frangula bark, alder buckthorn	Gastrointestinal	Frangulins	Anthraquinone glycoside
Rheum officinale, *Rheum* spp (Polygonaceae)	Rhubarb	Gastrointestinal	Rhein anthrones	Anthraquinone glycoside
Rheum spp (Polygonaceae)	Rhubarb species	Urologic	Oxalates	Carboxylic acid
Rhododendron spp (Ericaceae)[a]	Rhododendron	Cardiac, neurologic	Grayanotoxins	Terpenoid including resin and oleoresin
Ricinus communus (Euphorbiaceae)[a]	Castor or rosary seeds, tick seeds	Gastrointestinal	Ricin, curcin	Lectin
Robinia pseudacacia (Fabiaceae)[a]	Black locust	Gastrointestinal	Robinia lectin	Lectin

Rumex spp (Polygonaceae)	Dock species	Urologic	Oxalates	Carboxylic acid
Saintpaulia spp[b]	African violet	Nontoxic	Nontoxic	None
Salix spp (Salicaceae)	Willow species	Cinchonism	Salicin	Glycosides: other
Sambucus spp (Caprifoliaceae)	Elderberry	Metabolic	Anthracyanins	Cyanogenic glycoside
Sanguinaria canadensis (Papaveraceae)	Sanguinaria, bloodroot	Gastrointestinal	Sanguinarine	Alkaloid
Schefflera spp (Araceae)[b]	Umbrella tree	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Schlumbergera bridgesii[b]	Christmas cactus	Dermatitis: mechanical	Nontoxic	None
Senecio spp (Compositae/Asteraceae)[a]	Groundsel	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Sida carpinifolia (Malvaceae)	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
Sida cordifolia (Malvaceae)[a]	Bala	Cardiac, neurologic	Ephedrine and related compounds	Alkaloid
Solanum americanum (Solanaceae)[a]	American nightshade	Gastrointestinal, neurologic, some anticholinergic possible	Solasodine, soladulcidine, solanine, chaconine	Alkaloid
Solanum dulcamara (Solanaceae)[a,b]	Deadly nightshade, bitter nightshade	Gastrointestinal, neurologic, some anticholinergic possible	Solanine, chaconine, belladonna alkaloids, eg, atropine	Alkaloid
Solanum nigrum (Solanaceae)[a]	Black nightshade, common nightshade	Gastrointestinal, neurologic, some anticholinergic	Solanine, chaconine, belladonna alkaloids (atropine)	Alkaloid
Solarium tuberosum (Solanaceae)[a]	Potato (green)	Gastrointestinal, neurologic, some anticholinergic	Solanine, chaconine	Alkaloid
Spathiphyllum spp (Araceae)[b]	Peace lily	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Spinacia oleracea (Chenopodiaceae)	Spinach, others	Urologic	Oxalates	Carboxylic acid
Strychnos nux-vomica, S. ignatia (Loganiaceae)[a]	Nux vomica, Ignatia, St. Ignatius bean, vomit button	Neurologic	Strychnine and brucine	Alkaloid

(continued)

TABLE 114–4. Primary Toxicity of Common Important Plant Species *(continued)*

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Swainsonia spp (Fabiaceae)	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
Symphytum spp (Boragniaceae)[a]	Comfrey	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Tanacetum vulgare (= *Chrysanthemum vulgare*; Compositaceae/Asteraceae)[a]	Tansy	Neurologic	Thujone	Terpenoid
Taxus baccata, Taxus brevifolia, other *Taxus* spp (Taxaceae)[a]	English yew, Pacific yew, yew	Cardiac	Taxine	Alkaloid
Theobroma cacao (Sterculiaceae)	Cocoa	Cardiac, neurologic	Theobromine	Alkaloid
Thevetia peruviana[a]	Yellow oleander	Cardiac	Thevetin	Cardioactive steroid
Toxicodendron radicans, T. toxicarium, T. diversilobum, T. vernix, T. spp, many others (Anacardaceae)[b]	Poison ivy, oak, sumac, many others	Dermatitis: contact, allergic	Urushiol oleoresins	Terpenoid
Tribulus terrestris (Fabaceae)	Tribulus terrestris	Dermatitis: hepatogenous photosensitivity in animals	Steroidal saponins (aglycones: diosgenin, yamogenin)	Saponin glycoside
Trifolium pratense and other (Fabaceae/Legumaceae)	Red clover	Hematologic	Coumarin	Phenol or phenylpropanoid
Tussilago farfara (Compositae/Asteraceae)[a]	Coltsfoot	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Urginea maritima, U. indica[a]	Red, White, or Mediterranean squill, Indian squill	Cardiac	Scillaren A, B	Cardioactive steroid
Veratrum viride, V. album, V. californicum (Liliaceae)[a]	False hellebore, green hellebore, European hellbore, California hellbore	Cardiac	Veratridine	Alkaloid

Viscum album (Loranthaceae or Viscaceae)	European mistletoe	Gastrointestinal	Viscumin	Lectin
Wisteria floribunda (Fabiaceae)	Wisteria	Gastrointestinal	Cystatin	Lectin

[a]Reports of life-threatening effects from plant use.
[b]Plants reported commonly among calls to poison centers.

TABLE 114–5. Hyoscyamine and Hyoscine-Containing Plants

Latin Name	Common Name	Description	Distribution	Toxin
Atropa belladonna	Belladonna, deadly nightshade	Fleshy, erect stem; hairy leaves; purple flowers; purple-black many-seeded berry when ripe	Cultivated in Eastern states; rarely survives in wild form	Hyoscyamine, hyoscine
Cestrum nocturnum, Cestrum diurnum	Night-blooming jessamine; day-blooming jessamine	Large, attractive shrubs; fragrant small trumpet flowers; small berry	Coastal plains in South and Southwest	Saponins, gastroenterotoxins
Datura stramonium	Tolguacha, apple of Peru, jimsonweed, Jamestown weed, devil's apple, thorn apple, devil's trumpet, stinkweed, loco seeds, locoweed	Large erect plant; funnel-shaped white or purple flowers; spreading branches; hard, prickly, ovate, many-seeded fruit	Cultivated or uncultivated fields; widespread in the United States	Hyoscyamine (leaves, roots, seeds); hyoscine (roots)
Hyoscyamus niger	Henbane, black henbane	Tall, erect stem; multi-branched stem with fetid odor, yellowish flowers, encapsulated seeds	Weed in the United States	Hyoscyamine, hyoscine
Lycium halimifolium	Matrimony vine	Vine or shrub; bell-shaped flowers; ovoid orange-red berry	Northern United States	Hyoscyamine

Within these families, the genera *Heliotropium*, *Senecio*, and *Crotalaria*, respectively, are particularly notable for their content of toxic pyrrolizidine alkaloids. Chronic exposures cause hepatic venoocclusive disease by stimulating proliferation of the intima of hepatic vasculature.

Cardioactive Steroids

Poisoning by virtually all cardioactive steroids is clinically indistinguishable from poisoning by digoxin (Chap. 63), which is itself derived from *Digitalis lanata.* However, compared to toxicity from pharmaceutical digoxin, toxicity resulting from the cardioactive steroids found in plants will have markedly different pharmacokinetic characteristics. For example, digitoxin found in *Digitalis* species has a plasma half-life as long as 192 hours (average: 168 hours). Table 114–6 lists plants containing cardioactive steroids. (Also see Antidotes in Brief: Digoxin-Specific Fab.)

Glycyrrhizin

Glycyrrhizin is a saponin glycoside derived from *Glycyrrhiza glabra* (licorice) and other *Glycyrrhiza* species. Glycyrrhizin inhibits 11-hydroxysteroid dehydrogenase, an enzyme that converts cortisol to cortisone. When large amounts of licorice root are consumed chronically, cortisol levels rise, resulting in pseudohyperaldosteronism because of its affinity for renal mineralocorticoid receptors. Chronic use eventually leads to hypokalemia with muscle weakness, sodium and water retention, hypertension, and dysrhythmias (Chap. 17).

Cyanogenic Glycosides: (*S*)-Sambunigrin, Amygdalin, Linamarin, Cycasin

Cyanogenic glycosides yield hydrogen cyanide on complete hydrolysis. These glycosides are represented in a broad range of taxa and in about 2500 plant species. The species that are most important to humans are cassava (*Manihot esculenta*), which contains linamarin, and *Prunus* species, which contain amygdalin (Table 114–7).

Many North American species of plants contain consequential amounts of cyanogenic compounds. While the fleshy fruit of *Prunus* species in the Rosacea are nontoxic (apricots, peaches, pears, apples, and plums), the leaves, bark, and seed kernels contain amygdalin, which is metabolized to cyanide. The hallmarks of cyanide toxicity include a severe metabolic acidosis (lactate) with multiorgan

TABLE 114–6. Plants Containing Cardioactive Steroids

Apocyanaceae	Liliaceae
Nerium oleander (oleander)	*Convallaria majalis* (lily of the valley)
Strophanthus (dogbane)	*Urginea maritima*, *Urginea indica* (squill)
Thevetia peruviana spp (yellow oleander)	
Asclepiadaceae	
Asclepias (milkweed)	
Calotropis (crown flower)	
Celastraceae	Ranunculaceae
Euonymus europaeus (spindle tree)	*Helleborus niger* (henbane)
Cruciferae	Scrophulariaceae
Cheiranthus, *Erysimum* (wall flower)	*Digitalis purpurea*, *Digitalis lanata* (foxglove)

TABLE 144–7. Plants Containing a Cyanogenic Glycoside

Apple (seeds)	Jetberry bush (jet bead)
Apricot	Lima beans
Bamboo (sprouts of some species)	Mountain mahogany
Bitter almond	Peach
Cassava (beans and roots)	Pear (seeds)
Cherry laurel	Pin cherry
Christmas berry	Plum
Crab apple (seeds)	Western choke cherry
Choke cherry (stone fruit)	Wild black cherry
Elderberry (leaves and shoots)	
Hydrangea (leaves and buds)	

failure (Chap. 121 and Antidotes in Brief: Sodium Thiosulfate; Antidotes in Brief: Sodium and Amyl Nitrites; and Antidotes in Brief: Hydroxocobalamin).

Toxalbumins

Toxalbumins such as ricin and abrin are lectins that are such potent cytotoxins that they are used as biologic weapons (Chap. 127). Ricin, extracted from the castor bean (*Ricinus communis*), exerts its cytotoxicity by two separate mechanisms. The compound is a large molecule that consists of two polypeptide chains bound by disulfide bonds, and must enter the cell to exert its toxic effect. The B chain binds to the terminal galactose of cell surface glycolipids and glycoproteins. The bound toxin then undergoes endocytosis and is transported via endosomes to the Golgi apparatus and the endoplasmic reticulum. There the A chain is translocated to the cytosol, where it stops protein synthesis by inhibiting the 28S subunit of the 60S ribosome. In addition to the gastrointestinal manifestations of vomiting, diarrhea, and dehydration, ricin can cause cardiac, hematologic, hepatic, and renal toxicity. Other toxalbumin or toxalbuminlike–containing plants include *Abrus precatorius* (jequirity pea, rosary pea), *Jatropha* spp, *Trichosanthes* spp (eg, *kirilowii* or Chinese cucumber), *Robinia pseudoacacia* (black locust), *Phoradendron* spp (American mistletoe), *Viscum* spp (European mistletoe), and *Wisteria* spp (wisteria).

Oxalic Acid and Oxalate Raphides

Oxalic acid is the strongest acid among the carboxylic acids found in living organisms, and it forms poorly soluble chelates with calcium and other divalent cations. Higher plants vary in their ability to accumulate these products of metabolism. Oxalates are mainly found in certain plant families such as the Araceae, Chenopodiaceae, Polygonaceae, Amaranthaceae, and several of the grass families.

The insoluble calcium oxalate raphides that are present in certain plants, usually in the Araceae family, are found in conjunction with a protein toxin that increases the painful irritation to skin or mucous membranes. Ingestion results in rapid development of redness, swelling, and local pain in the mouth and throat. Immediate development of symptomatology limits exposure. Ocular exposure causes immediate intense pain, chemical conjunctivitis and corneal abrasions. Treatment involving demulcents (milk, ice cream, water) and cold packs are adequate; ocular exposure requires irrigation.

Cicutoxin

Cicutoxin, a diacetylenic diol, is found in the water hemlock, *Cicuta maculata,* and other *Cicuta* spp. Ingestion of any part of this plant constitutes the most common form of lethal plant ingestion in the United States. These ingestions usually involve adults who incorrectly identify the plant as wild parsnip, turnip, parsley, or ginseng. Symptoms of mild or early poisonings consist of gastrointestinal symptoms (nausea, vomiting, epigastric discomfort) and begin as early as 15 minutes after ingestion. Diaphoresis, flushing, dizziness, excessive salivation, bradycardia, hypotension, bronchial secretions with respiratory distress, and cyanosis occur, and rapidly progress to violent seizures.

Sodium Channel Effects: Aconitine, Veratridine, Zygacine, Taxine, and Grayanotoxins

Several unrelated plants produce toxins that affect the flow of sodium at the sodium channel. For instance, aconitine and veratrum alkaloids tend to open the channels to influx of sodium, whereas others, like taxine, tend to block the flow, and grayanotoxins both increase and block the flow of sodium. The sodium channel opener Aconitine from *Aconitum* spp or *Delphinium* spp has the most persistent toxicity and lowest therapeutic index among the many active alkaloid ingredients of the toxin called aconite. Suspicion of this ingredient should be raised in potentially poisoned patients who manifest cardiac toxicity, paresthesia, and seizures.

Ingestion of veratridine and other veratrum alkaloids (from *Veratrum viride* and other *Veratrum* spp) generally results from foraging errors where the root is similar in appearance to leeks (*Allium porrum*), and above ground parts similar to gentian (*Gentiana lutea*) used for teas and wines in Europe. The mechanism of action is like that of aconitine—sodium channel opening—but with shorter duration. Although severe toxicity is reported, management is supportive with fluids, atropine and pressors, and deaths are rare.

Grayanotoxins (formerly termed andromedotoxins) are a series of 18 toxic diterpenoids present in leaves of the various species of *Rhododendron*, *Azalea*, *Kalmia*, and *Leucothoe* (Ericaceae). They exert their toxic effects via sodium channels, which they open or close, depending on the toxin. Grayanotoxin I increases membrane permeability to sodium and affected calcium channels in a manner similar to that of veratridine. Grayanotoxins become concentrated in honey made from the above plants mainly in the Mediterranean. Bradycardia, hypotension, gastrointestinal manifestations, mental status changes ("mad honey"), or seizures are described in patients or animals suffering grayanotoxin toxicity.

Plant-Induced Dermatitis

A large number of plants result in undesirable dermal, mucous membrane, and ocular effects, and these are the most common of adverse effects reported to US poison centers and occupational health centers. Plant-induced dermal disorders may be categorized into four mechanistic groups, that is, dermatis that results from (a) mechanical injury; (b) irritant molecules that penetrate the skin; (c) allergy; and (d) photosensitivity.

The most important cause of dermatitis is poison ivy/poison oak (*Toxicodendron dermatitis*). Plants involved include *T. radicans* (poison ivy; not west coast); *T. toxicarium* (eastern poison oak), *T. diversilobum* (western poison

oak); and *T. vernix* (poison sumac). Similar toxins can be found in Mango rind and cashew nut shells. The toxin is a urushiol-containing oleoresin that produces a contact dermatitis characterized by pruritus and urticaria, erythema, edema, and bullae. The rash often takes a linear pattern from brushing against a twig or scratching with contaminated fingernails. Reactivity requires prior sensitization and most people can be sensitized; at least 50% of the population is sensitized, but reactivity to the toxin varies substantially between individuals. Ingestion and inhalation produce internal contact and reactions can be severe.

Removal from continued exposure by washing and the use of aluminum acetate solution or a lubricating agent such as petrolatum is sufficient for mild dermatitis. Topical steroids (hydrocortisone 1%) may also be helpful, but severe exposures require a course of oral corticosteroids.

115 Arthropods

The majority of arthropods are benign and environmentally beneficial. However, some spiders and ticks have toxic venoms that can produce dangerous, painful lesions or significant systemic effects. This chapter does not discuss infectious diseases transmitted by arthropods.

Arthropoda is the largest phylum in the animal kingdom, with at least 1.5 million species identified and half a million yet to be classified. Although most spiders are venomous, their chelicerae (jaw apparatuses) are too short to penetrate human skin. The species of medical importance include the widow spiders (*Latrodectus* spp), the violin spiders (*Loxosceles* spp), and the hobo spider (*Tegenaria agrestis*) in the United States. In Australia, the funnel web spider (*Atrax robustus*) can cause serious illness and death. In South America, the Brazilian Huntsmen (*Phoneutria fera*) and Arantia Armedeira (*Phoneutria nigriventer*) are threats to humans.

HISTORY AND EPIDEMIOLOGY

Approximately 200 species of spiders are associated with envenomations. From 1995–2003, there has been an annual average of 22,000 reported spider exposures and 50,000 insect exposures in the United States. There were no more than four fatalities reported per year.

BLACK WIDOW SPIDER (*LATRODECTUS MACTANS;* HOURGLASS SPIDER)

There are five species of widow spiders in the United States: *Latrodectus mactans* (black widow), *L. hesperus* (Western black widow), *L. variolus, L. bishopi* (brown widow), and *L. geometricus* (brown widow or brown button spider). Dangerous widow spiders in other parts of the world include *L. geometricus*, *L. mactans tredecimquttatus* (European widow spider); *L. mactans hasselti* (red-back widow spider found in Australia, Japan, and India); and *L. mactans cinctus* (South Africa). The ventral markings on the abdomen are species specific, and the classic red hourglass-shaped marking is noted in only the *L. mactans*. The female *L. mactans* is typically shiny, jet-black, large (8–10 mm), with a rounded abdomen and a red hourglass mark on its ventral surface. The venom is more potent on a volume-per-volume basis than that of a pit viper. α-Latrotoxin (the primary toxin in mammals) triggers a cascade of events that results in exocytosis of presynaptic neurotransmitters.

Clinical Manifestations

A sharp pain typically described as a pinprick occurs as the victim is bitten and a pair of red spots may evolve at the site. Muscle cramps typically present 15–60 minutes following the bite. Initially they occur at the site of the bite but may later involve rigidity of other skeletal muscles, particularly muscles of the chest, abdomen, and face. The pain increases over time and occurs in waves that may cause the patient to writhe. Additional clinical findings include *facies latrodectismica*, which describes the sweating, contorted, grimaced face associated with blepharitis, conjunctivitis, rhinitis, cheilitis, and trismus of the masseters. A fear of death,

pavor mortis, is also described. Life-threatening complications include severe hypertension, respiratory distress, cardiovascular failure, and gangrene. Nausea, vomiting, sweating, tachycardia, hypertension, and restlessness may also be present. Although recovery usually ensues within 24–48 hours, symptoms may last several days with more severe envenomations.

Diagnostic Testing

Laboratory data are generally not helpful in management or predicting outcome. There is currently no specific laboratory assay capable of confirming latrodectism.

Management

Treatment involves establishing an airway and supporting respiration and circulation if indicated. Wound evaluation and local wound care including tetanus prophylaxis are essential. The routine use of antibiotics is not recommended. Pain management is a substantial component of patient care. Mild envenomation may only require cold packs and orally administered nonsteroidal antiinflammatory agents. More severe envenomation will probably require intravenous opioids and benzodiazepines to control pain and muscle spasm. Intravenous infusion of calcium is generally ineffective.

Latrodectus antivenom is rapidly effective and curative. However, because antivenom is a crude hyperimmune horse serum, the risk of anaphylaxis is significant. Therefore the antivenom should only be considered for life-threatening reactions such as hypertensive crisis and intractable pain, or high-risk events, such as a pregnant woman suffering from a threatened abortion, or to treat priapism. The usual dose is 1–2 vials diluted in 50–100 mL of 5% dextrose or 0.9% NaCl solution and the combination is infused over 1 hour (see Antidotes in Brief: Antivenom [Scorpion and Spider]).

BROWN RECLUSE SPIDER (*LOXOSCELES RECLUSA*; VIOLIN OR FIDDLEBACK SPIDER)

Spiders in the genus *Loxosceles* have a worldwide distribution. In the United States, other species of this genus, which include *Loxosceles rufescens, L. deserta, L devia,* and *L. arizonica,* are prominent in the Southeast and Southwest. This small (6–20-mm long), gray to orange or reddish brown spider has a brown, violin-shaped mark on the dorsum of the cephalothorax.

Pathophysiology

The venom is cytotoxic and contains various enzymes, such as hyaluronidase, deoxyribonuclease, ribonuclease, alkaline phosphatase, lipase, and sphingomyelinase-D. Hyaluronidase is a spreading factor that facilitates the ability of the venom to penetrate tissue. Sphingomyelinase-D is the primary constituent of the venom that causes necrosis and hemolysis. Sphingomyelinase also triggers a chain reaction releasing inflammatory mediators such as thromboxanes, leukotrienes, prostaglandins, and neutrophils, which leads to vessel thrombosis, tissue ischemia, and skin loss.

Clinical Manifestations

The clinical spectrum of loxoscelism can be divided into three major categories. The first category includes bites that have very little, if any venom injected, and

there may be a localized urticarial response and a small erythematous papule that becomes firm before healing. In the second category, the bite undergoes a cytotoxic reaction. The bite, which may be initially painless or have a stinging sensation, blisters, bleeds, and then ulcerates 2–8 hours later. The lesion may increase in diameter, with demarcation of central hemorrhagic vesiculation, ulcerate, and develop violaceous necrosis, surrounding ischemic blanching of skin, and outer erythema and induration over 1–3 days. Necrosis of the central blister occurs in 3–4 days with eschar formation occurring between 5–7 days. After 7–14 days, the wound becomes indurated and the eschar falls off, leaving an ulceration that heals by secondary intention. Local necrosis is more extensive over fatty areas (thighs, buttocks, and abdomen). Large lesions up to 30 cm may take 4 months or longer to heal.

Systemic loxoscelism, which is not predicted by the extent of cutaneous reaction, is the third category and occurs 24–72 hours after the bite. The clinical manifestations include fever, chills, weakness, edema, nausea, vomiting, arthralgias, petechial eruptions, rhabdomyolysis, disseminated intravascular coagulation, hemolysis that can lead to hemoglobinemia, hemoglobinuria, renal failure, and death.

Diagnostic Testing

Bites from other spiders (such as *Tegenaria* spp; see below) and other insects can become necrotic wounds and are often the actual culprits when the brown recluse is mistakenly blamed. Definitive diagnosis is achieved only when the biting spider is positively identified. Standard laboratory data may be remarkable for hemolysis, hemoglobinuria, and hematuria. A coagulopathy may be present with elevated fibrin split products, decreased fibrinogen concentrations, a positive D-dimer assay and an increased prothrombin time (PT) and partial thromboplastin time (PTT).

Treatment

The optimal local treatment of the lesion is controversial. The most prudent management of the dermatonecrotic lesion is wound care, immobilization, tetanus prophylaxis, analgesics, and antipruritics, as warranted. Early excision or intralesional injections of corticosteroids appear unwarranted. Antibiotics should be used to treat cutaneous or systemic infection, but should not be used prophylactically. The early use of dapsone in patients who develop a central purplish bleb or vesicle within the first 6–8 hours may inhibit local infiltration of the wound by polymorphonuclear leukocytes. The dosage recommended is 100 mg twice a day for 2 weeks. However, prospective trials with large numbers of patients are lacking. If dapsone therapy is used, a baseline glucose-6-phosphate dehydrogenase and weekly complete blood counts should be performed.

HOBO SPIDER (*TEGENARIA AGRESTIS*, NORTHWESTERN BROWN SPIDER, WALCKENAER SPIDER)

The hobo spider is native to Europe and was introduced to the northwestern United States (Washington, Oregon, Idaho) in the 1920s or 1930s. It is brown with gray markings and 7–14 mm in length. The medical literature is sparse in reported hobo spider bites that are verified by a specialist. There is only one confirmed hobo spider bite resulting in a necrotic lesion. The patient complained of persistent pain, nausea, and dizziness, and a vesicular lesion developed within several hours, which ruptured and ulcerated the next day. The lesion was initially 2 mm and developed over the next 10 weeks up to a diameter of 30 mm, which was circumscribed with a black lesion. Other cases implicating the hobo spider as

a cause for dermatonecrotic injuries are based on proximity of the hobo spider or other large brown spider that is unidentified, and a rabbit-model bioassay.

Treatment

Treatment emphasizes local wound care and tetanus prophylaxis, although systemic corticosteroids for hematologic complications may be of value. Surgical graft repair for severe ulcerative lesions may be warranted when there is no additional progression of necrosis.

TARANTULAS

There are more than 1500 species of tarantula, with approximately 40 species found in the deserts of western United States. Their defense lies in either their painful bite with erect fangs or by spraying their victim with barbed urticating hairs that are released in provocation.

Tarantulas bite when provoked or roughly handled. Based on the few case reports, their venom has relatively minor effects for humans but can be deadly for canines and other small animals such as rats, mice, cats, and birds. Four genera of tarantulas (*Lasiodora, Grammostola, Acanthoscurria,* and *Brachypelma*) possess urticating hairs that are released in self-defense by rubbing their hind legs against their abdomen rapidly to create a small cloud. Tarantula hairs cause intense inflammation that may remain pruritic for weeks.

Clinical Manifestation

Although relatively infrequent in occurrence, bites may or may not present with puncture or fang marks and range from being painless to a deep throbbing pain that may last several hours without any inflammatory component. Fever is associated even in the absence of infection, suggesting a direct pyrexic action of the venom. Rarely, bites can also create a local histamine response with resultant itching, and hypersensitive individuals could have a more severe reaction and, rarely, mild systemic effects, such as nausea and vomiting. Contact reactions from the hairs are more likely to be the health hazard than the spider bite. These urticating hairs provoke local histamine reactions in humans and are especially irritating to the eyes, skin, and respiratory tract. Inflammation can occur at all levels—from the conjunctiva to retina—and an allergic rhinitis may also develop if the hairs are inhaled.

Treatment

Treatment is largely supportive. Cool compresses and analgesics should be given as needed. All bites should receive local wound care, including tetanus prophylaxis if necessary. If the hairs are barbed, as in some species, they can be removed by using adhesive or cellophane tape followed by compresses or irrigation with 0.9% sodium chloride solution. If the hairs are located in the eye, surgical removal may be required, followed by medical management of inflammation. Urticarial reactions should be treated with oral antihistamines and topical or systemic corticosteroids.

FUNNEL WEB SPIDERS

Australian funnel web spiders are a group of large mygalomorphs that can cause a severe neurotoxic envenomation syndrome in humans. The *Atrax* and

the *Hadronyche* species have been found along the eastern seaboard of Australia. *Atrax robustus*, otherwise known as the Sydney funnel web spider, is considered one of the most poisonous spiders.

Pathophysiology

Robustotoxin (atracotoxin or atraxin) is the main component of the venom. It produces an autonomic storm, releasing acetylcholine, noradrenaline, and adrenaline.

Clinical Manifestations

A biphasic envenomation syndrome is described. The first phase consists of localized pain at the bite site, perioral tingling, piloerection, and regional fasciculations (most prominent in the face, tongue, and intercostals). Fasciculations may progress to more overt muscle spasm; masseter and laryngeal involvement can threaten the airway. Other features include tachycardia, hypertension, dysrhythmias, nausea, vomiting, abdominal pain, diaphoresis, lacrimation, salivation, and acute lung injury, which is often the cause of death in this phase.

The second phase consists of resolution of the overt cholinergic and adrenergic crisis; secretions dry up, fasciculations, spasms, and hypertension resolve. The apparent improvement can be followed by the gradual onset of refractory hypotension, apnea, and cardiac arrest.

Treatment

Pressure immobilization may inactivate the venom and should be applied as *Atrax robustus* is one of the few animal toxins known to undergo local inactivation. Removal of the pressure immobilization should occur when the patient arrives at a facility that can administer antivenom. The starting dose of antivenom is 2 ampules if systemic signs are present and 4 ampules if the patient develops acute lung injury or depressed mental status. Doses are repeated every 15 minutes until clinical improvement is seen.

SCORPIONS

Scorpions are invertebrate arthropods that have existed for more than 400 million years. The poisonous scorpions in the United States are *Centruroides gertschii* and *C. exilicauda.* Unlike most spiders, scorpions envenomate humans by stinging rather than biting. Their five-segmented tail contains a bulbous segment called the telson that contains the venom apparatus.

Pathophysiology

Scorpions from the family Buthidae are the most harmful to humans. Their venom is thermostable, and consists of phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins. Components of the venom of the *C. exilicauda* are primarily neurotoxic. Some of the toxins target excitable membranes, especially at the neuromuscular junction, by opening sodium channels, resulting in repetitive depolarization of nerves in both sympathetic and parasympathetic nervous systems, causing acetylcholine and catecholamine release, increased neurotransmitter release, catecholamine release from the adrenal gland, catecholamine-induced cardiac hypoxia, and increased renin secretion at the juxtaglomerular apparatus.

Clinical Manifestations

Systemic effects may occur depending on the scorpion species involved. Scorpion stings produce a local reaction consisting of intense local pain, erythema, tingling or burning, and, occasionally, discoloration and necrosis without tissue sloughing. In the United States, *C. exilicauda* stings produce local paresthesia and pain that can be accentuated by tapping over the envenomated area (tap test) without local skin evidence of envenomation (Table 115–1).

Treatment

Because most envenomations do not produce severe effects, local wound care, including tetanus prophylaxis and pain management, is usually all that is warranted. Treatment emphasizes support of the airway, breathing, and circulation. Corticosteroids, antihistamines, and calcium have been administered without any known benefit. The severity of the envenomation dictates the need to use antivenom. Continuous intravenous midazolam infusion has been used for *C. exilicauda* envenomation until resolution of the abnormal motor activity and agitation. One grading system suggests using antivenom for severe grade III and grade IV envenomations (see Antidotes in Brief: Antivenom [Scorpion and Spider]).

TICKS

In 1912, Todd described a progressive ascending flaccid paralysis after bites from ticks. In North America, the *Dermacentor andersoni* (North American wood tick) and *D. variabilis* are most commonly implicated in causing tick paralysis, whereas in Australia, the *Ixodes holocyclus,* or Australian marsupial tick, is the most common offender.

TABLE 115–1. Envenomation Gradation for *Centruroides exilicauda* (Bark Scorpion)

Grade	Signs and Symptoms
I	Site of envenomation: Pain and/or paresthesias Positive tap test (severe pain increase with touch or percussion)
II	Grade I plus Pain and paresthesias remote from sting site (eg, paresthesias moving up an extremity, perioral "numbness")
III	One of the following: Somatic skeletal neuromuscular dysfunction: jerking of extremity(s), restlessness, severe involuntary shaking and jerking, which may be mistaken for seizures Cranial nerve dysfunction: Blurred vision, wandering eye movements, hypersalivation, trouble swallowing, tongue fasciculation, upper airway dysfunction, slurred speech
IV	Both cranial nerve dysfunction and somatic skeletal neuromuscular dysfunction

Modified with permission from Curry SC, Vance MV, Ryan PJ, et al: Envenomation by the scorpion Centruroides sculpturatus. J Toxicol Clin Toxicol 1983–1984;21:417–448; Allen C: Arachnid Envenomations. Emerg Med Clin North Am 1992;10:269–298.

Pathophysiology

Venom secreted from the salivary glands during the blood meal is absorbed by the host and systemically distributed. Paralysis is caused by a neurotoxin, "ixovotoxin," that inhibits the release of acetylcholine at the neuromuscular junction and autonomic ganglia, in a manner similar to the botulinum toxin.

Clinical Manifestations

Usually the tick must remain on the person for 5–6 days to cause systemic symptoms. Several days must pass before tick salivary glands begin to secrete significant quantities of toxin and the toxin does not act immediately following secretion and may undergo binding and internalization in a similar sequence to botulinum toxin. Children may appear listless, weak, ataxic, and irritable for several days before developing an ascending paralysis beginning in the lower limbs. Fever is usually absent. Other symptoms include sensory symptoms such as paresthesias, numbness, mild diarrhea, followed by absent or decreased deep tendon reflexes. In addition, an ascending generalized weakness that can progress to bulbar structures involving speech, swallowing, and facial expression, develops within 24–48 hours, as well as fixed dilated pupils and disturbances of extraocular movements. If the tick is not removed, respiratory weakness can lead to hypoventilation, lethargy, coma, and death.

Treatment

The most important aspect of treatment is to entertain tick paralysis in the differential of any patient with ascending paralysis. Other than removal of the entire tick, which is curative, treatment is entirely supportive.

HYMENOPTERA: BEES, WASPS, HORNETS, YELLOW JACKETS, AND ANTS

Within the order *Hymenoptera*, there are three families of clinical significance: *Apidae* (honeybees and bumblebees), *Vespidae* (yellow jackets, hornets, and wasps), and *Formicidae* (fire ants). Insects of this subclass are of great medical importance, since their stings are the most commonly reported and can cause acute toxic and fatal allergic reactions (Table 115–2).

Pathophysiology

Several allergens and pharmacologically active compounds are found in honeybee venom. The three major venom proteins for the honeybee are melittin, phospholipase A_2, and hyaluronidase. Phospholipase A_2 represents the major antigen/allergen in bee venom, whereas melittin acts as a detergent to disrupt the cell membrane and liberate potassium and biogenic amines. Histamine release by bee venom appears to be largely mediated by mast cell degranulation peptide.

Clinical Manifestations

Normally, the honeybee sting is manifested as immediate pain, a wheal-and-flare reaction, and localized edema without a systemic reaction. With a higher dose of venom as a result of multiple stings, vomiting, diarrhea, and syncope can occur. Toxic reactions occur with multiple stings (greater than 500 stings are described as possibly fatal) and include GI symptoms, headache, fever,

TABLE 115–2. Classification of Reactions to Hymenoptera Sting

Reaction	Clinical Presentation
Local	
Minimal	Localized pain, pruritus, swelling Lesion ≤5 cm Duration several hours
Large	Localized pain and pruritus Contiguous swelling and erythema Lesion >5 cm Duration 1–3 days
Systemic	
Minimal	Localized pain, pruritus, swelling Distant and diffuse urticaria, angioedema, pruritus and/or erythema, conjunctivitis Abdominal pain, nausea, diarrhea
Severe	Dermatologic Local: Pain, pruritus, and swelling Distant: Urticaria, angioedema, pruritus, and/or erythema Gastrointestinal Nausea, abdominal pain, diarrhea Respiratory Nasal congestion, rhinorrhea, hoarseness, bronchospasm, stridor, tachypnea, cough, wheezing Cardiovascular Tachycardia, hypotension, dysrhythmias, myocardial infarction Miscellaneous Seizures, feeling of impending doom, uterine contractions

Reprinted with permission from Sinkinson CA, French RS, Graft DF, ads: Individualizing therapy for Hymenoptera stings. Emerg Med Rep 1990;11:134.

syncope and, rarely, rhabdomyolysis, renal failure, and seizures. Bronchospasm and urticaria are typically absent, differentiating this type of reaction from the more common hypersensitivity reactions or anaphylactic reactions.

Treatment

Application of ice at the site is usually sufficient to halt discomfort. The stinger should be removed. Therapy is aimed at supportive care. Anaphylaxis should be treated with epinephrine, histamine antagonists, and corticosteroids, as for any other cause.

FIRE ANTS

There are native fire ants in the United States, but the imported fire ants *Solenopsis invicta* and *S. richteri* are significant pests that have no natural enemies. *S. invicta*, the most aggressive species, now infests 13 southern states. Fire ants range from 2–6 mm in size and live in grassy areas, gardens, and sites near still and flowing water. The nests are largely subterranean and are conspicuous large dome-shaped above-the-ground mounds (up to 45 cm above the ground) with many openings for traffic. Fire ants are named for the burning pain inflicted after an exposure that can also result in necrosis at the

site. The imported fire ant attacks with little warning, firmly grasping the skin with its mandibles, repeatedly injecting venom from a retractile stinger at the end of the abdomen. Pivoting at the head, the fire ant injects an average of 7 or 8 stings in a circular pattern.

Pathophysiology

The venom, which inhibits Na^+–K^+–ATPase sodium and potassium adenosine triphosphatases, reduces mitochondrial respiration, uncouples oxidative phosphorylation, adversely affects neutrophil and platelet function, inhibits nitric oxide synthetase, and perhaps activates coagulation.

Clinical Manifestations

Local reactions occur in individuals without prior sensitization. Large local reactions are defined as painful, pruritic swelling at least 5 cm in diameter that are contiguous with the sting site. The sting initially forms a wheal that is described as a burning itch at the site followed by the development of sterile pustules. In 24 hours, the pustules umbilicate on an erythematous base. Pustules may last 1–2 weeks.

Diagnosis

There are no laboratory assays to determine exposure.

Treatment

Local reactions require cold compresses and cleansing with soap and water. Some authors recommend topical or injected lidocaine with or without 1:100,000 epinephrine and topical vinegar and salt mixtures to decrease pain at the site of the bite and sting. Large local reactions can be treated with oral corticosteroids, antihistamines, and analgesics.

BUTTERFLIES, MOTHS, AND CATERPILLARS

Butterflies and moths are insects of the order *Lepidoptera*. There are several moth and butterfly families that contain spines or urticating hairs that secrete a poison that is irritating to humans on contact. In the United States, the puss caterpillar (*Megalopyge opercularis*) is often considered the most important and toxic of the caterpillars. In South America, especially Brazil, the *Lonomia obliqua* caterpillars are notorious for causing severe pain and a hemorrhagic syndrome.

Pathophysiology

Little is known about the composition of the venom and it probably varies with the different caterpillar species. Some toxins contain proteins that cause histamine release. Another protein isolated from the *L. olbiqua* caterpillar causes coagulopathy; although its mechanism of action is still fully unknown, it somehow activates factors X and II.

Clinical Manifestations

The clinical effects of caterpillar exposure can generally be separated into two types of reactions, although overlap may occur: the stinging and the pru-

ritic reactions. Stinging caterpillars, such as the *M. opercularis*, envenomate by contact from their hollow spines containing venom. It is characterized as a painful, burning sensation with local effects and, less commonly, systemic effects. The area may become erythematous and swollen, and papules and vesicles may appear. The classic gridlike pattern develops within 2–3 hours of contact. Pruritic reactions occur following exposure to the itchy caterpillars that have nonvenomous urticating hairs, which can produce a mechanical irritation, allergic reaction, or a granulomatous reaction from the chronic presence of the hairs.

Treatment

Treatment for dermal contact should be immediate, with removal of the embedded spines using cellophane tape and application of ice. If minor analgesics fail to control the pain, opioids may be necessary. If muscle cramps develop, benzodiazepines should be administered. Topical corticosteroids can be used to decrease local inflammation. Antihistamines such as diphenhydramine (25–50 mg for adults and 1 mg/kg, maximum 50 mg in children) may be used to relieve pruritus and urticaria. In the case of a hemorrhagic syndrome from exposure to the *L. olbiqua,* an antilonomic serum (SALon) is available.

BLISTER BEETLES

Blister beetles are plant-eating insects that exude a blistering agent. They can be found in the eastern United States, southern Europe, Africa, and Asia. When the beetle senses danger, it exudes cantharidin by filling its breathing tubes with air, closing its breathing pores, and building up body fluid pressure until fluid is pushed out through one or more leg joints. Cantharidin, also known popularly as "Spanish fly," has been used as a sexual stimulant. The aphrodisiac properties are related to cantharidin's ability to cause vascular engorgement and inflammation of the genitourinary tract, hence the reports of priapism and pelvic organ engorgement. Cantharidin poisoning is reported by cutaneous exposure, unintentional inoculation, and inadvertent ingestion of the beetle itself.

Pathophysiology

Although the mechanism of action has not been elucidated, one possible mechanism suggests that cantharidin inhibits the activity of protein phosphatases types 1 and 2A. This inhibition alters endothelial permeability by enhancing the phosphorylation state of endothelial regulatory proteins and results in elevated albumin flux and dysfunction of the barrier.

Clinical Manifestations

The clinical effects can mostly be attributed to the irritative effects on the exposed organ systems. The secretions cause an urticarial dermatitis that is manifested several hours later by burns, blisters, or vesiculobullae. Symptoms may be immediate or delayed over several hours. In addition to the local effects, cantharidin can cause systemic toxicity with diaphoresis, tachycardia, hematuria, and oliguria from an extensive dermal exposure. When ingested, severe GI disturbances and hematuria can occur. Initial patient complaints may include burning of the oropharynx, dysphagia, abdominal cramping, vomiting, and hematemesis followed by lower GI tract symptoms of hematochezia and tenesmus.

Diagnostic Testing

Cantharidin toxicosis has been identified by screening urine and gastric contents with high-performance liquid chromatography and gas chromatography–mass spectrometry. This method has not been used for clinical practice.

Treatment

Treatment is largely supportive. Wound care and tetanus prophylaxis status should be assessed. For a keratoconjunctivitis, consult an ophthalmologist early in the clinical course and start the patient on topical corticosteroids (prednisolone 0.125%), mydriatics (cyclopentolate 1%), and antibiotics (ciprofloxacin 0.3%).

Antivenom (Scorpion and Spider)

The terms *antivenom* and *antivenin* are often used interchangeably. Except where it refers to a specific brand name, the term *antivenom* is used in this Antidotes in Brief. Antivenom for spiders and scorpions is prepared by immunizing animals with venom and then collecting the immune serum for administration.

The exact identity of the species of arachnid is rarely known in the clinical setting. The spider or scorpion specimen is not usually available. The species is usually inferred more from the geographic region where the injury occurred than from the clinical presentation. Occasionally, stings or bites have resulted from scorpions or spiders in imported rugs and fruit. The clinician must also be aware that professional and amateur entomologists may be exposed to bites or stings from exotic species, although, in these instances, the exact genus and species, or at least the common name, is usually known.

CENTRUROIDES SPECIES

Centruroides exilicauda (formerly known as *C. sculpturatus*) is the only native scorpion of medical importance in the United States. At one time the mortality from scorpion envenomation in the United States was twice as high as that of all other venomous animals combined. Although the incidence of envenomation remains high, no deaths associated with the toxic effects of scorpion venom have occurred for more than 40 years. The low incidence of fatalities is most likely attributable to better methods of supportive care, as well as the use of antivenom and the development of pediatric intensive care units.

Antivenom for the *Centruroides* species was produced in Mexico, in horses, as early as the 1930s. The Antivenom Production Laboratory at Arizona State University (APL-ASU) began producing antivenom to *C. exilicauda* in goats in 1965, and this product was the antivenom in use for treatment of scorpion stings in Arizona until November 2004. Production of the APL-ASU antivenom has since ceased. Although all stockpiles have expired, several hospitals retain vials of antivenom in their inventory. In view of the limited mortality from envenomation and the risk of serious immediate hypersensitivity or serum sickness from the administration of antivenom, there was rarely, if ever, an absolute indication for administration of *Centruroides* scorpion antivenom. Consequently, administration of antivenom was reserved for patients with the most severe envenomations, typically in children younger than age 6 years.

In Mexico, two antivenoms are primarily directed toward neutralizing the venom of *Centruroides* species. Neither is commercially available in the U.S. In June 2000, Silanes laboratory received orphan drug status for Alacramyn, an equine derived $F(ab)_2$ from *C. limpidus*, *C. noxius, C. suffusus suffusus,* and *C. meisei* (formerly known as *C. elegans*). Currently, clinical trials of $F(ab)_2$ use in envenomed children are underway, stimulated by the absence of the APL-ASU product. One vial of Alacramyn contains enough $F(ab)_2$ to neutralize 150 mouse LD_{50} (median lethal dose for 50% of test subjects) of *Centruroides* venom. It is administered by slow IV infusion, one vial at a time, with observation for 30–60 minutes before repeating. The incidence of allergic reactions to Alacramyn, is reported to be 2.7%. The average duration of symptoms in patients following treatment was 1.4 hours, compared to 15–24 hours in untreated

patients. Alacramyn is tentatively to be marketed under the name Anascorp in the U.S.

LATRODECTUS SPECIES (*LATRODECTUS MACTANS, L. HESPERUS, L. BISHOPI, L. GEOMETRICUS, L. INDISTINCTUS*)

The administration of the black widow spider antivenom is controversial. Although black widow envenomation is associated with severe muscle pain, cramping, and autonomic disturbances, mortality is low. Symptomatic treatment can almost always be accomplished with muscle relaxants and opioids, individually or in combination. Some authors believe that antivenom has too high a risk-to-benefit ratio to justify its use. In selected patients, however, the use of antivenom may reduce pain and suffering, shorten the course of the envenomation, and reduce or eliminate the need for hospitalization. We believe that indications for antivenom administration include severe muscle cramping, hypertension, diaphoresis, nausea, vomiting, and respiratory difficulty that is unresponsive to other therapy.

In North America, Antivenin (Merck and Co.) for black widow (*L. mactans*) venom is made by immunizing horses. Each vial of Antivenin contains 6000 Antivenin units standardized by biologic assay in mice. Because the venoms of *Latrodectus* species are virtually identical by immunologic and electrophoretic mechanisms, antivenom created for *L. mactans* is presumed to be effective in other species of *Latrodectus* as well.

In a review of 163 cases of presumed *L. hesperus* envenomations, antivenom reduced the duration of symptoms from a mean of 22 hours to a mean of 9 hours. Symptoms usually subsided within 1–3 hours of administration of the antivenom. Hospital admission rate fell from 52% in those who were managed with opioids and muscle relaxants to 12% in those patients receiving antivenom.

Dosage of antivenin (Merck and Co.) is usually 1 vial (2.5 mL) diluted in 50 mL of saline for intravenous administration. Despite the apparent efficacy of antivenom, the decision to give horse serum for a disease with limited mortality is of great concern. Death from bronchospasm and anaphylaxis is reported as a complication of antivenom administration, as is serum sickness.

Funnel Web Spider (*Atrax* and *Hadronyche*) Envenomation

A rabbit IgG-based funnel-web spider antivenom is available in Australia. Since its introduction, no deaths have been reported. The initial dose should be 2 ampules in patients with any signs of envenomation; patients with evidence of acute lung injury or decreased consciousness should receive 4 ampules. The dosage for children is the same as for adults.

In severe envenomations the following protocol should be used. Two ampules (each 5 mL) of antivenom should be administered very slowly intravenously (adult or child). That dose can be repeated in 15 minutes if there is no improvement. The dose should be doubled for a severe case. A rapid response should occur. The administration of antivenom should be repeated until symptoms are completely reversed. It is not uncommon for *Atrax robustus* envenomations to require more than 3 ampules of antivenom.

116 Marine Envenomations

Human encounters with venomous marine creatures are commonplace and can result in serious clinical effects. Injuries may arise from direct toxic effects, as well as from mechanical destruction caused by the stinging apparatus. Significant morbidity and mortality have occurred following envenomation with spiny fish, cone snails, octopi, sea snakes, and several species of jellyfish.

INVERTEBRATES

Cnidaria

Members of the phylum *Cnidaria* (formerly *Coelenterata*) are commonly referred to as "jellyfish." All species possess microscopic cnidae, which are highly specialized organelles consisting of an encapsulated, hollow, barbed thread bathed in venom. Thousands of these stinging organelles, called nematocysts (or cnidoblasts), are distributed along tentacles. Penetration of flesh leads to hypodermic venom delivery. Although nematocysts of most *Cnidaria* are incapable of penetrating human skin, life-threatening and even lethal envenomation does result from a few species.

Cubozoa

Members of the class *Cubozoa* have a cube-shaped bell with 4 corners, each of which supports between 1 and 15 tentacles. Species from this order produce the greatest morbidity and mortality of all *Cnidaria*. Two main families are of toxicologic importance: *Chirodropidae* and *Carybdeidae.*

The *Chirodropidae* family is known for the box jellyfish, *Chironex fleckeri*. When full-grown, its bell measures 25–30 cm in diameter and has 15 tentacles attached at each bell corner. These tentacles may extend up to 3 m in length. Another member of this family is *Chiropsalmus quadrigatus*, the sea wasp. Its pale blue color makes detection in the water nearly impossible.

The *Carybdeidae* family is most notable for *Carukia barnesi*, the Irukandji jellyfish. Its small size, with a bell diameter of 2.5 cm, also makes detection in the water difficult.

Hydrozoa

The *Hydrozoa* class are capable of inflicting considerable pain and even death in humans. The order *Siphonophora* (*Physaliidae* family) includes *Physalia physalis*, the Portuguese man-of-war, and its smaller counterpart, *P. utriculus*, the bluebottle. They exist as a colony and are easily recognizable by a blue sail that floats above the water's surface. Tentacles of *P. physalis* may reach lengths in excess of 30.5 m and contain over 750,000 nematocysts in each of its numerous tentacles (up to 40). *P. utriculus* has only one tentacle, which measures up to 15 m.

The *Milleporina* order is well known for the sessile *Millepora alcicornis* (fire coral), which also exists as a colony of hydroids. It appears much like true coral and has a white to yellow-green lime carbonate exoskeleton. Small tentacles protrude through minute surface gastropores. The overall structure ranges from 10 cm to 2 m.

Scyphozoa

Jellyfish belonging to the class *Scyphozoa* and are extremely diverse in size, shape, and color. Common varieties known to envenomate humans are *Cyanea capillata* (Lion's mane or hair jelly), *Chrysaora quinquecirrha* (sea nettle), and *Pelagia noctiluca* (mauve stinger). The mauve stinger is easily recognized, as it appears pink in daylight and phosphorescent at night. Larvae of certain *Linuche linguiculata* cause sea bather's eruption (SBE).

Anthozoa

The *Anthozoa* class has a diverse membership that includes true corals, soft corals, and anemones. Only the anemones are of toxicologic concern.

History and Epidemiology

Stings from *Cnidaria* represent the overwhelming majority of marine envenomations. In Australia, approximately 10,000 stings per year caused by the *Physalia* spp alone are recorded. Since 1884 the estimated number of deaths in Australia attributed to *C. fleckeri* is approximately 70. An estimated 2–3 deaths occur each year in Malaysia. Approximately 20–40 deaths are reported yearly in the Philippines, and 3 deaths are well documented from *P. physalis* in the United States. Cases of SBE, a stinging rash from *Cnidaria* larvae, occur in clusters. In 1992, more than 10,000 cases of SBE occurred in south Florida, with similar peaks in the 1940s and 1960s. Cases of SBE are also reported in Cuba, Mexico, the Caribbean, and, occasionally, in Long Island, NY.

Pathophysiology

Cnidaria venoms can induce dermatonecrosis, myonecrosis, hemolysis, or cardiotoxicity, depending on the particular species. In rats, *C. fleckeri* venom transiently elevates blood pressure, but hypotension and cardiovascular collapse follow in minutes. Other effects include decreased inotropy, cardiac conduction delay, ventricular tachycardia, and decreased coronary artery flow. Two myotoxins from *C. fleckeri* cause powerful, sustained muscle contractions in isolated muscle fibers. *C. barnesi*, the Irukandji jellyfish, likely induces its dramatic vasopressor effects via catecholamine release. In rats this can be blocked by α_1-adrenergic receptor antagonism. Venom from *Physalia* spp blocks neural impulses, produces ventricular ectopy, cardiovascular collapse, hyperkalemia, and hemolysis. *Physalia* spp venom inhibits Ca^{2+} entry into the sarcoplasmic reticulum.

Symptoms resulting from stings may be partly immune mediated. Elevated serum anti-sea nettle IgM, IgG, and IgE concentrations may persist for years in patients with exaggerated reactions to stings compared to controls. SBE displays a characteristic delay in onset of symptoms and can be effectively treated with steroids, suggesting a primary immune-mediated process for this entity. This is further supported on histopathology by the presence of perivascular and interstitial infiltrates with inflammatory cells.

Clinical Manifestations

The vast majority of patients who seek medical care after being stung have severe pain, but are not systemically poisoned. However, severe systemic manifestations may develop following stings from *C. fleckeri*, *C. barnesi*, *P. physalis*, and a few other *Cnidaria.* Envenomation by *C. fleckeri* causes the

most severe pain and systemic toxicity. Common symptoms include immediate severe pain followed by an erythematous whiplike linear rash with a "frosted ladder" appearance. Systemic symptoms include nausea, vomiting, muscle spasms, headache, malaise, fever, chills, vertigo, ataxia, paralysis, delirium, syncope, and respiratory distress. Hypotension, dysrhythmias, pulmonary edema, hemolysis, and acute renal failure occur in severe cases. Some estimates cite a fatality rate following *C. fleckeri* envenomation of 15–20%, but this is probably an overestimation. Fatality is documented following as little as 4 m of tentacle markings. Death is typically rapid, leaving many victims unable to reach shore.

Irukandji syndrome is often associated with a mild sting and skin findings are typically absent. Severe systemic symptoms develop within 30 minutes and mimic a catecholamine surge: tachycardia, palpitations, hyperpnea, headache, pallor, restlessness, apprehension, sweating, and a sense of impending doom. A prominent feature is severe, whole-body muscle spasms that come in waves and preferentially affect the back. Hypertension is universal and may be severe; fatalities seem to result from consequences of severe hypertension such as intracranial hemorrhage. Hypotension frequently follows, requiring vasopressor support. Pulmonary edema results from myocardial dysfunction.

P. physalis envenomation typically causes severe pain along with bullae and skin necrosis. Systemic symptoms include weakness, numbness, anxiety, headache, abdominal and back spasms, lacrimation, nasal discharge, diaphoresis, vertigo, hemolysis, cyanosis, renal failure, shock, and, rarely, death.

M. alcicornis (fire coral) produces far less significant injuries. It is a nuisance to divers who touch what they perceive to be harmless coral and suffer moderate burning pain for hours. Untreated pain generally lessens within 90 minutes, with skin wheals flattening at 24 hours and resolving within a week. Hyperpigmentation may persist up to 8 weeks.

Skin lesions of SBE develop within hours of itching and appear as discrete, closely spaced papules, with pustules, vesicles, and urticaria. Most lesions occur in areas covered by the bathing suit; however, folds of skin, such as the axilla, breasts, and neck, may be affected. Systemic symptoms, such as chills, headache, nausea, vomiting, and malaise, may occur.

Diagnostic Testing

Venom assays are not available and serum antibody titers are not clinically useful. Laboratory evaluation may be warranted in patients suffering systemic toxicity following *Cnidaria* envenomation. Victims of Irukandji stings and others with consequential cardiovascular toxicity should have serial measurement of serum cardiac markers. Following severe stings from a variety of *Cnidaria*, urinalysis, hematocrit, and serum creatinine should be considered to detect the presence of hemolysis and subsequent renal injury. Chest radiography is indicated for complaints of dyspnea or abnormalities in oxygenation.

Management

Initial interventions follow standard management strategies. Secondary measures are directed toward the prevention of further nematocyst discharge. Although vinegar is a common first-line agent for topical application following most *Cnidaria* stings, including the box jelly fish, it is generally ineffectual, although potentially harmful in some. In many cases, the identity of the "jellyfish" causing injury is unknown. Therapy in that case must be guided by geographic location. In the United States, where *P. physalis* and *C. quinquecirrha*

are of greatest consequence, sea water should be used to aid in tentacle removal, given that vinegar enhances nematocyst discharge. In the Indo-Pacific region, where *C. fleckeri* and *C. barnesi* are of greatest concern, vinegar should be the primary agent used. Following a 30-second application, adherent tentacles must be carefully removed with a gloved or towel-covered hand, or with sand and gentle scraping with a credit card or other blunt, straight-edged tool. Ice packs may provide effective relief for patients with mild to moderate pain from *Cnidaria* stings; hot water is ineffective for venom neutralization and can increase pain.

Box jellyfish antivenom is sheep-derived whole IgG raised against the "milked" venom of *C. fleckeri*. Pretreatment of rats with box jellyfish antivenom prevented cardiovascular collapse in 40% of animals. There are no controlled studies in humans evaluating the efficacy of box jellyfish antivenom in the treatment of *C. fleckeri* envenomations, nor is there convincing evidence that its use has saved human lives. Although box jellyfish antivenom use may improve pain control, patients may still require parenteral opioids for analgesia following its administration, and significant morbidity and mortality still occur despite its use.

The manufacturer recommends treating initially with 1 ampule IV diluted 1:10 with saline or 3 undiluted ampules (1.5–4 mL each) IM at three separate sites if IV access is unavailable. Some authors who have treated multiple patients with antivenom suggest treating coma, dysrhythmias, or respiratory depression with 1 ampule IV, titrating up to 3 ampules with continuation of cardiopulmonary resuscitation (CPR) in patients with refractory dysrhythmias, until a total of 6 ampules have been administered. For less serious envenomations, patients may receive 1 ampule if ice packs and parenteral opioids prove ineffective.

Treatments for Irukandji syndrome should focus on analgesia and blood pressure control. Several modalities for control of severe hypertension have been suggested, including intravenous phentolamine, magnesium, and nitroglycerin.

Mollusca

The phylum *Mollusca* (Latin *mollis* = soft) includes the classes *Cephalopoda* (octopus, squid, and cuttlefish) and *Gastropoda* (cone snails). Of the cephalopods, only the blue-ringed octopus, *Hapalochlaena maculosa*, and greater blue-ringed octopus, *H. lunulata,* are of toxicologic concern. The genus *Conus* has 400 species of cone snails, 18 of which are implicated in human envenomations.

History and Epidemiology

A review of reported octopus envenomations uncovered a total of 14 cases (two fatal), all of which occurred in Australia. Recent estimates of reported cone snail envenomations suggest only 15 deaths have occurred worldwide.

Pathophysiology

The octopus salivary gland secretes tetrodotoxin. Tetrodotoxin blocks Na^+ conductance in neurons, leading to paralysis. Death from hypotension may occur despite respiratory support.

Cone snails have a hollow proboscis that contains a tooth bathed in venom. Any given *Conus* species contains about 100 peptides or conotoxins in its venom. Targets include voltage- and ligand-gated ion channels, as well as G-protein linked receptors.

Clinical Manifestations

The blue-ringed octopus creates one or two puncture wounds with its chitinous jaws, causing only a small amount of discomfort. A wheal may develop with erythema, tenderness, and pruritus. Symptoms develop rapidly and include perioral and intraoral paresthesias, diplopia, aphonia, dysphagia, ataxia, weakness, nausea, vomiting, flaccid muscle paralysis, respiratory failure, and death.

Envenomation ranges from a slight stinging sensation to excruciating pain. Local symptoms include tissue ischemia, cyanosis, and numbness. Systemic symptoms include weakness, diaphoresis, diplopia, blurred vision, aphonia, dysphagia, generalized muscle paralysis, respiratory failure, cardiovascular collapse, and coma. Death is rapid and occurs within 2 hours.

Diagnostic Testing

Laboratory testing following envenomation from octopi or cone snails should be directed by clinical findings. Tetrodotoxin may be detected in the urine or serum using high-performance liquid chromatography with subsequent fluorescence detection; however, this assay is not readily available.

Management

Primary interventions include maintenance of airway, breathing, and circulation. Some authors recommend hot water immersion (113–122°F [45–50°C]) following cone snail stings for pain relief. Other measures include local wound care and tetanus prophylaxis.

Echinodermata, Annelida,* and *Porifera

The *Echinodermata* phylum includes starfish, brittle stars, sea urchins, sand dollars, and sea cucumbers. *Annelida* are segmented worms, which include the *Polychaetae* family of bristle worms. Sponges are classified in the *Porifera* phylum. All three phyla passively envenomate people who mistakenly handle or step on them. Most stings from these creatures are mild.

History and Epidemiology

Echinoderms, annelids, and sponges are ubiquitous ocean inhabitants. Data in the incidence of envenomation are lacking.

Pathophysiology

Sea urchins are covered in spines and pedicellariae, both of which contain venom. Venom consists of steroid glycosides, 5-hydroxytryptamine (5-HT), hemolysin, protease, and acetylcholinelike substances. Some species harbor neurotoxins. Sea cucumbers excrete holothurin, a sulfated triterpenoid oligoglycoside as a defense. The toxin inhibits neural conduction in fish, leading to paralysis. Bristle worm bristles lead to envenomation with an unknown substance.

Clinical Manifestations

Most injuries from sea urchins are caused by inadvertently stepping on the spines or attempting to handle the animal. An intense burning with local tissue reaction occurs, including edema and erythema. Other effects are anecdotal. The crown-of-thorns may cause severe pain, nausea, vomiting, and muscular paralysis. Handling sea cucumbers leads to contact dermatitis, intense corneal inflammation, and even blindness. Bristle worms are covered in

irritating bristles that can cause a reddened urticarial rash. Contact with the fire sponge, poison-bun sponge, or red-moss sponge causes erythema, papules, vesicles, and bullae, which generally subside within 3–7 days.

Management

The primary objective following envenomation from sea urchins and crown-of-thorns starfish is analgesia. Submersion of the affected extremity in hot water (105–115°F [40.6–46.1°C]) is commonly used. Puncture wounds require radiographic evaluation to locate potential foreign bodies. Tetanus prophylaxis should be addressed. Consideration of antibiotic prophylaxis should be based on degree of injury and patient factors. Although most infections are likely secondary to human skin flora, marine flora such as *Mycobacterium marinum* and *Vibrio parahaemolyticus* should be considered potential wound contaminants.

VERTEBRATES

Snakes

Sea snakes are members of the class *Reptilia* that are close relatives of the cobra and krait. They are generally less than 1 m in length, have a flattened tail, and are often brightly colored. Distinction from eels is made by the presence of scales and the absence of fins and gills. There are 52 species of sea snakes, all of which are venomous. At least six species are implicated in human fatalities. The most common species cited in human envenomation is *Enhydrina schistosa*, the beaked sea snake. *Pelamis platurus*, the yellow-bellied sea snake, is also frequently implicated.

History and Epidemiology

Sea snakes are common to the tropical and temperate Indian and Pacific Oceans, but are also found along the eastern Pacific Coast of Central and South America and the Gulf of California. There are no sea snakes in the Atlantic Ocean. The true incidence of sea snake envenomation is unknown, as many bites go unreported. The number of deaths per year worldwide may approach 150, with an overall mortality rate estimated at 3%.

Pathophysiology

All sea snakes have small front fangs. Their venom is neurotoxic, myotoxic, nephrotoxic, and hemolytic. Known components of the venom include acetylcholinesterase, hyaluronidase, leucine aminopeptidase, 5′-nucleotidase, phosphodiesterase, and phospholipase A. The neurotoxin is similar to that of the cobra and krait, but beaked sea snake venom is 4–5 times more potent. The neurotoxin acts postsynaptically via acetylcholine (ACh) receptor blockade at the neuromuscular junction and presynaptically causes initial release of ACh followed by inhibition of ACh release.

Clinical Manifestations

Bites are typically painless or inflict minimal discomfort. Symptom onset may occur within minutes, although a delay of up to 6 hours is possible. Although paralysis results from the neurotoxic fraction of the venom, muscle destruction stemming from myotoxic fractions causes painful, stiff muscle movements and myoglobinuria, which are hallmarks of sea snake myotoxicity. Myoglobinuria develops between 30 minutes and 8 hours after the bite.

Other symptoms include ascending flaccid paralysis, dysphagia, trismus, ptosis, aphonia, nausea, vomiting, fasciculations, and, ultimately, respiratory insufficiency, seizures, and coma.

Diagnostic Testing

Laboratory diagnostics are directed toward identifying hemolysis, myonecrosis, hyperkalemia, and renal failure. Serum electrolytes, creatinine, and creatine phosphokinase, as well as hematocrit and urinalysis should be obtained.

Management

Prehospital management of sea snake bites includes immobilization of the extremity and consideration of a pressure immobilization bandage to impede lymphatic drainage. Airway and respiratory effort should be closely monitored as paralysis can develop rapidly. The most commonly used antivenoms for sea snakes are equine IgG Fab fragments derived from the beaked sea snake (*E. schistosa*) or terrestrial tiger snake (*Notechis scutatus*). The manufacturer's guidelines for use of monovalent sea snake antivenom recommend administration of 1 vial (1000 units) for systemic symptoms. The antivenom should be diluted 1:10 with saline and administered IV over 30 minutes. Epinephrine and antihistamines should be readily available. No upper limit is suggested for the number of vials to administer, although larger amounts are more likely to result in serum sickness. Patients have received up to 7000 units without adverse effect directly attributable to the antivenom. One vial (3000 units) of tiger snake antivenom may be used as an alternative if sea snake antivenom is unavailable.

Fish

Stingrays are members of the class *Chondrichthyes* (order *Rajiformes:* skates and rays). The family *Scorpaenidae* is comprised of a variety of venomous spiny fish. Fish in the genus *Pterois* are commonly called lionfish (*P. volitans* and *P. lunulata*). Stonefish are grouped under the genus *Synanceja* and include *S. trachynis* (Australian estuarine stonefish), *S. horrida* (Indian stonefish), and *S. verrucosa* (reef stonefish). Scorpionfish have a similar appearance and belong to the genus *Scorpaena* (eg, *S. guttata* [California sculpin]). Other *Scorpaenidae* include *Notesthes robusta* (bullrout) and *Gymnapistes marmoratus* (cobbler). The European weeverfish causes toxicity similar to members of *Scorpaenidae,* and is classified under the family *Trachinidae*.

History and Epidemiology

Some estimates suggest 1500–2000 stingray injuries occur yearly in the United States. Most envenomations occur when the animal is inadvertently stepped on. In a recent review, 17 fatalities were identified worldwide resulting from trunk wounds, hemorrhage, or tetanus. No deaths stemming solely from venom are recorded. Three populations are at highest risk for spiny fish envenomation: fishermen sorting the catch from nets, waders, and aquarium enthusiasts. Only five poorly documented deaths have ever been reported from *Scorpaenidae*, all of which resulted from stonefish. The incidence of weeverfish stings is unknown, but a review identified approximately 12 cases per year resulting in "serious illness" in one locale. Lionfish are common in home aquariums and account for most poison center calls involving spiny fish envenomation in the United States.

Pathophysiology

Stingray tails possess tapered, bilaterally retroserrated spines covered by an integumentary sheath. The venom glands saturate the spine in venom that contains several amino acids, 5-HT, 5-nucleotidase, and phosphodiesterase. In animal models, venom induces local vasoconstriction, bradydysrhythmias, atrioventricular nodal block, subendocardial ischemia, seizures, coma, cardiovascular collapse, and death.

Scorpaenidae have 12–13 dorsal, 2 pelvic, and 3 anal spines that are covered with an integumentary sheath. Three main toxins have been isolated from various species of stonefish: stonustoxin (SNTX), verrucotoxin (VTX), and trachynilysin (TLY). Toxicity in animals includes hemolysis, local edema, vascular permeability, platelet aggregation, endothelium-dependent vasodilation, and hypotension. Decreased myocardial contractility occurs in rabbits. VTX blocks cardiac calcium channels. TLY forms pores in cell membranes, allows Ca^{2+} entry and causes Ca^{2+}-dependent release of acetylcholine from nerve endings at motor endplates and increased catecholamine release.

Clinical Manifestations

Stepping on the body of a stingray causes a reflexive whip of the tail, leading to wounds in the lower extremity. Intense pain disproportionate to the wound is characteristic. Symptoms peak at 30–90 minutes after injury and may persist for 48 hours. Local edema, cyanosis, erythema, and petechiae may follow rapidly and may lead to necrosis and ulceration. Systemic symptoms include weakness, nausea, vomiting, diarrhea, vertigo, headache, muscle cramps, fasciculations, hypotension, syncope, seizures, and dysrhythmias.

Stings from stonefish produce immediate severe pain with rapid wound cyanosis and edema, which may progress up the injured extremity. Pain reaches a maximum after 30–90 minutes and usually resolves over 6–12 hours, although pain may persist for days. Systemic symptoms may include headache, vomiting, abdominal pain, delirium, seizures, limb paralysis, hypertension, dysrhythmias, congestive heart failure, hypotension, and respiratory distress.

Reported symptoms from *P. volitans* envenomation include pain, swelling, nausea, numbness, joint pain, anxiety, headache, dizziness, and cellulitis. Systemic signs (nausea, diaphoresis, dyspnea, chest pain, abdominal pain, weakness, hypotension, and syncope) occur in approximately 13% of patients. Stings from weeverfish are clinically similar to *Scorpaenidae* envenomation.

Management

Wounds caused by stingrays and spiny fish should be carefully examined for imbedded foreign material. Radiographs may uncover occult spines left behind in the wound. Stingray wounds can be extensive and require surgical repair. Tetanus prophylaxis should be addressed and antibiotics may be appropriate for some injuries. Heating stonefish venom to 122°F (50°C) for 5 minutes prevents wound necrosis and hypotensive effects in animal models. In a series of stings from *P. pterois* and *S. guttata,* 80% of patients had complete relief with hot water. Success with using hot water is also reported with weeverfish stings and stingray envenomation. If relief is not sufficient, oral or parenteral analgesia may be required.

Stonefish antivenom is an equine-derived IgG Fab fragment. Anecdotal reports suggest it provides effective relief from pain. The manufacturer recom-

mends IM administration, although IV administration may be considered. Administration is indicated for systemic toxicity or pain not controlled with hot water and opioid analgesics. Dosing is guided by the number of puncture wounds sustained: 1 vial for 1–2 punctures, 2 vials for 3–4 punctures, and 3 vials for 5 or more punctures. Epinephrine and diphenhydramine should be readily available for anaphylactic reactions.

117 Snakes and Other Reptiles

EPIDEMIOLOGY

Incidence of Venomous Snakebites in the United States

Venomous snakes are found throughout the United States, except Maine, Alaska, and Hawaii. They are common in the Appalachian states, the South, and the West, but are rare in colder states. Because snakes hibernate in the winter, most bites in the United States occur between May and October. There are approximately 6000–8000 venomous snakebites per year in the U.S. and many thousands more from nonvenomous species. Mortality from snakebites is considered to be quite rare in the United States, with estimates ranging from 5–15 deaths per year. Children, intoxicated individuals (mostly men), snake handlers, and collectors are frequent victims.

Identification of a Venomous Snake

There are 120 species of snakes native to North America, including approximately 30 venomous species (Table 117–1). Most of these venomous snakes are members of the family Viperidae (subfamily Crotalinae), which include the rattlesnakes (*Crotalus* and *Sistrurus*) along with the copperheads and water moccasins (*Agkistrodon*). The other family of venomous snakes native to the United States is the Elapidae, which includes the coral snakes. The vast majority of venomous snake bites in the United States are from pit vipers.

The venomous Crotalinae in the United States have a triangular-shaped head, vertically elliptical pupils, and easily identifiable fangs (Fig. 117–1).

The coral snakes (*Micruroides* and *Micrurus* species) are the brightly colored Elapids, having easily identifiable red, yellow, and black bands along the length of their body. Coral snakes have black snouts, whereas king snakes have red snouts. Both species have red, yellow, and black rings, but in different sequences. The red and yellow rings touch in the coral snake but in king snakes are separated by black rings ("Red on yellow kills a fellow, red on black, venom lack").

Exact identification of a snake is often not possible unless the victim brings the offending reptile to the hospital. This is usually impossible and poses an additional threat to the victim or prehospital personnel. Knowledge of the indigenous venomous snakes is often helpful to medical personnel.

PHARMACOLOGY OF VENOM

Crotaline venom is a complex heterogeneous solution and suspension of various proteins, peptides, lipids, carbohydrates, and enzymes. Numerous unidentified proteolytic enzymes, procoagulants and anticoagulants, cardiotoxins, hemotoxins, and neurotoxins abound in crotaline venom, making it very complex to analyze. Crotaline venom can simultaneously damage tissue directly, affect blood vessels and cellular elements of blood, and alter the myoneural junction and nerve transmission. Venom is present in the circulation, as well as fixed to tissues.

Coral snake venom consists of a number of unidentified neurotoxins with curarelike effects that produce systemic neurotoxicity as opposed to local tissue injury.

TABLE 117–1. Scientific and Common Names of Medically Important Venomous Snakes of North America

Scientific Name	Common Name
Crotalinae (Pit Vipers)	
Rattlesnakes	
Crotalus adamanteus	Eastern diamondback
Crotalus atrox	Western diamondback
Crotalus cerastes cerastes	Mojave Desert sidewinder
Crotalus cerastes cercobombus	Sonoran Desert sidewinder
Crotalus horridus horridus	Timber
Crotalus horridus atricaudatus	Canebrake
Crotalus molossus molossus	Northern blacktail
Crotalus ruber ruber	Red diamond
Crotalus scutulatus scutulatus	Mojave
Crotalus viridis cerberus	Arizona black
Crotalus viridis relleri	Southern Pacific
Crotalus viridis lutosus	Great Basin
Crotalus viridis oreganus	Northern Pacific
Crotalus viridis viridis	Prairie
Sistrurus catenatus catenatus	Eastern massasauga
Sistrurus catenatus edwardsi	Desert massasauga
Sistrurus catenatus tergeminus	Western massasauga
Sistrurus millarius millarius	Carolina pigmy
Other Pit Vipers	
Agkistrodon contortrix contortrix	Southern copperhead
Agkistrodon contortrix laticinctus	Broad-banded copperhead
Agkistrodon contortrix mokason	Northern copperhead
Agkistrodon piscivorus conanti	Florida cottonmouth
Agkistrodon piscivorus piscivorus	Eastern cottonmouth
Agkistrodon piscivorus leucostoma	Western cottonmouth
Bothrops atrox	Fer-de-lance
Elapidae (Coral Snakes)	
Micruroides euryxanthus	Sonoran coral snake
Micrurus fulvius fulvius	Eastern coral snake
Micrurus fulvius tenere	Texas coral snake

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Crotaline Envenomation

The severity and clinical manifestations of envenomation depend on a number of factors, including number of strikes, depth of envenomation, size of the snake, potency and amount of venom injected, size and underlying health of the victim, and location of the bite. Larger snakes generally inject more venom. Children and small adults, as well as those with underlying medical conditions (diabetes mellitus, cardiovascular disease), may be more seriously affected by envenomation.

Local Reactions

Pit vipers produce a characteristic bite when they strike, and distinct fang marks can usually be identified. Fang marks can be single, double, or, occasionally, multiple.

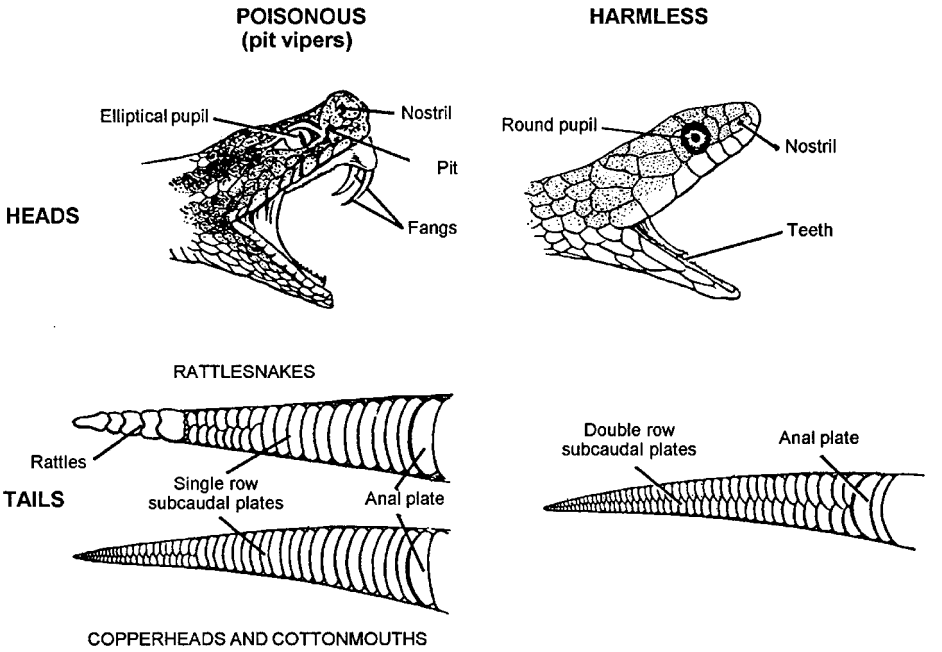

FIG. 117–1. Features of pit vipers and harmless snakes. *(Modified and reprinted with permission from Parrish HM, Carr CA: Bites by copperheads in the United States. JAMA 1967;201:927.)*

Crotaline (pit viper) venom is usually injected only into the subcutaneous tissue, although deeper, intramuscular (subfascial) envenomation does (rarely) occur. Not every bite releases venom; so-called dry bites occur in up to 20% of strikes. Symptoms may range from mild to severe, but the initial benign presentation of a pit viper bite can be very misleading (Table 117–2). Compared with the venom of rattlesnakes, the venom of water moccasins (cottonmouths) produces less-severe local and systemic pathology, and envenomation from copperheads tends to be less severe than that of either rattlesnakes or water moccasins.

Envenomation is a dynamic and ever-changing process that can rapidly and unpredictably progress to serious local or systemic involvement. It may require a number of hours for the full extent of envenomation to become evident. As a general rule, however, it may be assumed that if no symptoms develop within 8–12 hours from the time of the bite, envenomation from a North American pit viper has not occurred (dry bite).

Systemic Signs

When venom is injected subcutaneously, it travels by lymphatic and superficial venous channels and spreads rather slowly to reach the general circulation. It generally requires a number of hours for subcutaneous envenomation to produce systemic symptoms, but this timetable is quite variable. Intravascular envenomation produces significant systemic symptoms in a matter of minutes. Systemic signs often include nonspecific weakness, malaise, nausea, and restlessness. More severe envenomation produces confusion, abdominal pain, vomiting, diarrhea, sweating, dyspnea, tachycardia, hypotension, blurred vision, salivation, and a metallic taste in the mouth. Rarely, patients may exhibit disseminated intravascular coagulation (DIC) with spontaneous bleeding, along with significant hypotension and multiorgan system failure. Although local tissue destruction dominates most crotaline envenomations, neurotoxic effects occur with the Mojave rattlesnake (*Crotalus scutulatus scutulatus*).

Hematologic

Significant crotaline envenomation may produce complex and dramatic hematologic abnormalities secondary to the effects of the venom on the blood coagulation pathways, endothelial cells, and platelets. Fibrinogen concentrations drop and the platelet count falls. The prothrombin time (PT) and partial thromboplastin time (PTT) are prolonged and frequently unmeasurable.

Anaphylaxis

Rarely, a patient bitten by a crotaline may experience anaphylaxis from the venom itself. This can complicate evaluation or mimic a severe systemic reaction to venom. The presence of pruritus and urticaria or wheezing, which is uncommon with envenomation, suggests anaphylaxis. The symptoms respond to standard treatment for anaphylaxis (epinephrine, antihistamines, and corticosteroids).

Elapid Envenomation

The severe local reaction to crotaline envenomation is in contrast with the usually minor pain and clinically unimpressive local reactions that occur with a coral snake bite. Coral snake envenomation may be manifested by serious

TABLE 117–2. Evaluation and Treatment of Crotaline Envenomation

Extent of Envenomation	Clinical Observations	Antivenom Recommendation[a]	Other Treatment	Disposition
None ("dry bite")	Fang marks may be seen, but no local or systemic symptoms after 8–12 hours	None	Local wound care Tetanus prophylaxis	Discharge after 8–12 hours of observation
Minimal	Minor local swelling and discomfort only, with no systemic symptoms or hematologic abnormalities	None	Local wound care Tetanus prophylaxis	Admit to monitored unit for 24-hour observation
Moderate	Progression of swelling beyond area of bite, with local tissue destruction, hematologic abnormalities, or systemic symptoms	Yes	IV fluids Cardiac monitoring Analgesics Follow laboratory values Tetanus prophylaxis	Admit to ICU
Severe	Marked progressive swelling and pain, with blisters, bruising, and necrosis; systemic symptoms such as vomiting, fasciculations, weakness, tachycardia, hypotension, and severe coagulopathy	Yes	IV fluids Cardiac monitoring Analgesics Follow laboratory values Oxygen Vasopressors PRN Tetanus prophylaxis	Admit to ICU

[a]See Antidotes in Depth: Antivenom (Crotaline and Elapid), for dosing recommendations.

systemic reactions with little symptomatology at the actual site of envenomation, even after an asymptomatic period of up to 12 hours.

Systemic Effects

The systemic effects of elapid envenomation are characteristically delayed for a number of hours (Table 117–3). Patients can develop total body paralysis that may last 3–5 days and take weeks to resolve completely. With respiratory support, however, the paralysis is completely reversible. Pulmonary aspiration is a common sequela in the subacute phase.

MANAGEMENT

The initial objectives are to determine the presence or absence of envenomation, to provide basic supportive therapy, to treat the local and systemic effects of envenomation, and to limit or repair tissue loss and/or functional disability. A combination of medical therapy that includes supportive care, antivenom when warranted, and conservative surgical treatment using débridement of devitalized tissue when indicated, as individualized for each patient, is likely to provide appropriate results. In general, the faster treatment is instituted, the better the final outcome.

Observation of Asymptomatic Patients

A prudent approach is to observe all victims of possible crotaline bites for at least 8–12 hours after the bite and admit those with any evidence of envenomation. Eastern coral snake bites can be misleading because of an absence of early symptomatology. Serious delayed neurologic and respiratory symptoms have been specifically noted, so patients bitten by these snakes should be observed for 24 hours regardless of initial presenting symptoms.

Initial Treatment

No first aid measures or specific field treatment is proven to positively affect the outcome from a crotaline envenomation. Prehospital care should gener-

TABLE 117–3. Signs and Symptoms of Envenomation by the Eastern Coral Snake (*Micrurus fulvius*) (N = 20)

Sign or Symptom	Percent
Fang marks	85
Local swelling	40
Paresthesias	35
Nausea	30
Vomiting	25
Euphoria	15
Weakness	15
Dizziness	10
Diplopia	10
Dyspnea	10
Diaphoresis	10
Muscle tenderness	10
Fasciculations	5
Confusion	5

Reprinted, with permission, from Kitchens CS, Van Mierop LHS: Envenomation by the eastern coral snake (*Micrurus fulvius*): A study of 39 victims. JAMA 1987;258:1615.

ally be limited to immobilization of the patient's affected limb and rapid transport to a medical facility. Physical activity, such as walking, should be avoided because this may hasten systemic absorption of venom. Standard advanced cardiac life support (ACLS) protocols should be followed by prehospital personnel for the rare, unstable, snake bite victim.

A constriction band is not a true tourniquet; if it is applied properly, a finger may be easily placed between the band and the skin. There is evidence that a broad, firm, constrictive wrap (elastic bandage) placed over the bitten area and encircling the entire immobilized limb will slow the systemic absorption of venom and improve outcome of neurotoxic envenomations. We do not recommend pressure immobilization in management of North American pit viper envenomations. Likewise, incision and suction, whether by mouth or by commercially available device cannot be recommended as standard first aid in the field or on arrival to the hospital.

Immediate In-Hospital Therapy

A complete medical history, including current tetanus immunization status and known allergies, should be obtained. A careful description of the bite and the extent of the local pathology should be documented, including measuring the diameter of the extremity and noting the extent of edema by marking the skin with a pen to help recognize progression of the envenomation. This evaluation should be repeated as required by the clinical condition. A comprehensive physical examination should be done. A baseline complete blood count (CBC) and platelet count, electrolytes, urinalysis, BUN, glucose, PT, PTT, and fibrinogen concentration should be obtained initially and repeated in 4–6 hours.

Pain and anxiety should be treated with analgesics and anxiolytics as clinically warranted, and tetanus prophylaxis should be addressed. The extremity should be immobilized in a well-padded splint in near-full extension and elevated to avoid dependent edema. The patient should be reassessed frequently, specifically noting any progression of swelling.

Antivenom Therapy

For crotaline envenomations, antivenom should be considered as first-line therapy for those patients with moderate to severe envenomations (Table 117–2). Antivenom given in a timely manner can reverse the coagulopathy and halt progression of local symptoms. Antivenom therapy is discussed in more detail in Antidotes in Brief: Antivenom (Crotaline and Elapid).

Surgical Therapy

Envenomation may mimic a compartment syndrome by producing distal paresthesias, tense soft-tissue swelling, pain on passive stretch of muscles within a compartment, and muscular weakness. However, because subfascial envenomation is uncommon, true compartment compromise is rare. A compartment syndrome cannot be reliably diagnosed in envenomated extremities without directly measuring compartment pressures. Although there is little doubt that some crotaline bites may eventually require surgical débridement or even skin grafting, the initial routine use of tissue excision, fasciotomy, or "exploration and débridement" is not recommended.

Blood Products

Abnormal laboratory results, such as immeasurably low fibrinogen concentrations, PT greater than 100 seconds, and platelet counts less than 20,000/mm^3 are routinely encountered, and such abnormal results alone should not prompt the clinician to treat with blood products in the absence of major bleeding. Correction of laboratory coagulation abnormalities and bleeding can frequently be achieved with antivenom. The criteria for the use of blood products appears to be quite arbitrary in clinical practice, but in general, blood products should be administered along with antivenom only if the patient is actively bleeding.

Treatment of Coral Snake Envenomation

The benign local effects of coral snake envenomation can be misleading and mistakenly equated with a dry bite. Because it is difficult to judge initially which patients are envenomated, any patient with confirmed coral snake exposure with fang marks or other evidence of skin penetration should receive antivenom therapy even in the absence of symptoms.

Other Considerations

Tetanus prophylaxis should be administered and hyperimmune tetanus antitoxin given if there is inadequate primary immunization, or if the history is uncertain. Prophylactic antibiotics are not needed, as studies show extremely low (0–3%) rates of wound infections. No rationale supports the use of corticosteroids or antihistamines.

Recurrence Phenomena of Crotaline Envenomation

Definite recurrent local and coagulopathic effects, in the form of worsening of symptoms after initial clinical improvement following antivenom, are described. The recurrence phenomena are attributed to the interrelated kinetics and dynamics of venom and antivenom. Simply stated, Fab antivenom has a clinical half-life shorter than that of venom, and once tissue injury and coagulation deficits have been halted or corrected, there may be a worsening of tissue injury and coagulopathies unless additional antivenom is administered.

Nonvenomous Snakebites

Most of the approximately 50,000 snakebites that occur annually in the United States are from nonvenomous snakes. The wound should be cleansed, any foreign material removed, and an appropriate dressing applied. Certain large snakes of the Boidae family (not seen in the United States, except as pets or in zoologic gardens), including boas, pythons, and anacondas, may present a special problem because the force of contraction of their jaws may be great enough to cause severe tissue contusion or fractures and retained teeth. These reptiles have numerous large, brittle teeth that commonly are broken off and lodged in the wound when the bitten part is forcibly extricated from the snake's mouth. Usually radiographs of the bitten area are needed to exclude fracture or foreign body. A cogent argument can be made for administering prophylactic antibiotics in nonvenomous snakebites if tooth fragments are retained or if there is significant soft tissue contusion. A first-generation cephalosporin or antistaphylococcal penicillin given for 7–10 days should be adequate.

Bites from Exotic Snakes

Approximately 3% of poisonous snakebites in the United States are from nonnative species. Exotic venomous snakes pose a particularly difficult problem in both diagnosis and management. Once the snake is identified, the antivenom must be obtained. This is always a formidable task and often impossible, but local zoos, poison centers, or collectors may have the antivenom. Some poison centers, some zoos, and The American Association of Zoological Parks and Aquariums (301-562-0777) maintain the Antivenom Index, a listing of available antivenoms for exotic snakes, but these resources are limited in their ability to deliver many antivenoms. Guidelines for the administration of antivenom for exotic snakes are vague and empiric. Because exotic snakes are generally quite poisonous, if fang marks are present, envenomation is strongly suspected, the snake has been identified, and the specific antivenom has been obtained, many physicians believe that it is logical to proceed with antivenom administration empirically.

Other Poisonous Reptiles in the United States

In North America there are two indigenous species of venomous lizards: the Gila monster (*Heloderma suspectum*) and the beaded lizard (*H. horridum*). These lizards are found primarily in the desert areas of Arizona, southwestern Utah, southern Nevada, New Mexico, California, and Mexico. They are generally shy creatures, so bites are relatively rare, usually unintentional or secondary to handling. Gila monsters are known for their forceful bite and propensity to hang on tenaciously during a bite and may be difficult to disengage. Gila monster venom is complex, containing components similar to those of snake venoms, including numerous enzymes, hyaluronidase, phospholipase A, kallikrein, and serotonin. Their venom delivery systems are not as efficient as those of poisonous snakes and dry bites often occur. Following skin puncture and venom release, the victim experiences local tenderness and soft-tissue swelling, pain, and edema. Significant tissue destruction is unusual, but maceration may occur. Because no antivenom is available, treatment consists of supportive care and wound care. The characteristics of the beaded lizard are similar, but their bites are less commonly confronted clinically.

Other Venomous or Poisonous Animals

Several species of mammals contain venomous members. For example, the male Australian duckbilled platypus (*Ornithorhynchus anatinus*) has a hollow spur that may inject venom, and the Cuban insectivore (*Solenodon paradoxus*) and North American short-tailed shrew both secrete venom from the maxillary glands and bite with the lower incisors. Envenomations from mammals are quite rare, and little is known about the specific clinical toxicity from these creatures.

Several species of amphibians, frogs, toads (*Anura*), newts, and salamanders (*Urodela*) can secrete toxins through their skins, which may be a defensive repellant or alarm mechanism. The best-known examples are the Colombian poison dart frogs (*Phyllobates* and *Atelopus*), which secrete the toxins zetekitoxin, tetrodotoxin, and batrachotoxin. Batrachotoxin irreversibly activates (depolarizes) the sodium channel and is 250 times more toxic than curare in mice. Newts of the genus *Taricha* contain the irreversible sodium channel blocking agent tetrodotoxin in their skin and internal organs. Venom from toad species of the genus *Bufo* contains a number of toxic substances, including biogenic amines (serotonin), steroids, and polypeptides. A lysergic acid diethylamide (LSD)-like high is reported, but there is considerable folklore and confusion on the exact effects.

Antivenom (Crotaline and Elapid)

For decades, Wyeth Laboratories (Marietta, PA) manufactured the only crotaline antivenom to treat snakebites in the United States. It is a whole immunoglobulin product derived from horse serum. In October 2000, a refined crotaline antivenom (CroFab, Protherics, Savage Laboratories) derived from sheep and designed to be a less allergenic alternative than horse serum products became available. Because of safety issues, CroFab has become the antivenom of choice in most instances. One aspect of crotaline therapy that has not yet been clearly evaluated is a cost-to-benefit analysis comparing the two antivenoms, although it is clear that drug acquisition costs are higher for CroFab. Wyeth also produces a coral snake antivenom effective against the Eastern and Texas coral snakes.

Crotaline antivenom is given to ameliorate the effects of local and systemic envenomation by pit vipers, and it is considered by some clinicians to be lifesaving. Animal studies document a decrease in mortality when antivenom is given immediately after envenomation. Delay lessens the beneficial effects. Prospective human studies demonstrate that antivenom halts progression of local tissue swelling and reverses systemic effects, including most coagulation and platelet defects.

Because many crotaline snakebites will not require therapy, antivenom should not be given "prophylactically" to patients with minimal symptoms or to those who demonstrate no evidence of envenomation. The major indications for crotaline antivenom therapy are (a) rapid progression of swelling, (b) significant coagulopathy or thrombocytopenia, (c) neuromuscular toxicity, or (d) hemodynamic compromise. Standard doses for both antivenoms are described below. No dosing adjustment is required for children or small adults because the amount of venom requiring neutralization is not dependent on the patient's weight.

CROTALINE POLYVALENT IMMUNE FAB ANTIVENOM (OVINE ORIGIN)

CroFab polyvalent ovine-derived antivenom is obtained by inoculating sheep with the venom of the Eastern and Western diamondback rattlesnakes (*Crotalus adamanteus* and *C. atrox*), the cottonmouth (*Agkistrodon piscivorus*), and the Mojave Desert rattlesnake (*C. scutulatus*). The manufacturing process includes papain digestion of isolated IgG antibodies to eliminate the Fc portion of the immunoglobulin and to isolate specific antibody fragments [Fab and $F(ab)_2$], as well as, affinity purification and lyophilization. The Fab fragments have a smaller molecular weight, are less immunogenic, and may have increased tissue penetration compared to whole IgG. In preliminary studies, the number of severe acute and chronic hypersensitivity reactions associated with CroFab use was significantly reduced as compared with horse serum products, but clinical experience is still limited. Urticaria, rash, bronchospasm, pruritus, angioedema, delayed serum sickness, and anaphylaxis are all associated with this product. The same precautions that were used in the past with whole-immunoglobulin antivenoms should be practiced with the Fab product.

The pharmacokinetics and pharmacodynamics of Fab antivenom differ from those of other antivenoms. The duration of action of the CroFab antivenom appears to be less than that of traditional equine-derived polyvalent

antivenom. The elimination half-life of 12–23 hours is also less than that of the venom itself, so periodic or repeat dosing of Fab antivenom is required to prevent or treat recurrent symptoms.

Technique of Administration

A thorough history regarding asthma, atopy, concurrent use of β-adrenergic antagonists, allergy to papaya or papain, and previous use of antivenoms should be elicited. According to the manufacturer, the only absolute contraindication to CroFab use is allergy to papaya or papain, which is a contaminant of the manufacturing process. The other conditions do not exclude the use of antivenom if the patient is suffering from a moderate to severe envenomation; they just require a refined risk-to-benefit analysis.

Prior to drug infusion, an intravenous epinephrine infusion (250 mL of 5% dextrose in water [D_5W] mixed with 1 mg of epinephrine), 1–2 mg/kg of methylprednisolone, 0.5–1 mg/kg of diphenhydramine, and an H_2 antihistamine receptor blocker are placed at the patient's bedside. Antivenom is always administered in a monitored unit where resuscitation can be performed and airway supplies are quickly accessed. Each vial of CroFab must be reconstituted in 10 mL of sterile saline prior to use. A continuous gentle swirl or rolling method expedites reconstitution. Shaking and other vigorous methods should be avoided. Four to six vials of the reconstituted antivenom are then mixed in 250 mL of 0.9% NaCl solution and administered over 1 hour. For children, the total volume of fluid may be decreased when necessary. The infusion is begun at 10 mL/h and doubled every few minutes as tolerated. If no adverse reactions are witnessed, the remaining dose can be given over 1 hour. If the patient tolerates the initial dose without adverse effects, subsequent doses can be given over 1 hour without slowly increasing the rate.

When antivenom is administered too rapidly, mast cells release histamine and produce nonimmunogenically mediated anaphylactoid reactions. In general, patients appear to tolerate 4–6 vials an hour without developing anaphylactoid reactions. For acute anaphylactic reactions (which often occur shortly following initiation of even low doses of antivenom), the antivenom should be stopped and intravenous steroids, H_1 and H_2 antihistamine receptor blockers, and epinephrine given. The epinephrine may be initiated at 2–4 μg/min (0.03–0.06 μg/kg/min for children) and then titrated to effect. Only those patients at high risk for significant morbidity or mortality from snake envenomation should have the antivenom restarted after symptoms of hypersensitivity resolve. In such cases, the antivenom infusion is restarted at 1–2 mL/h while continuing the epinephrine infusion and slowly increased as tolerated.

After studying CroFab in two preclinical trials, the therapeutic regimen was empirically determined as illustrated in Figure A33–1. "Control" is defined as arrest of local tissue manifestations and return of coagulation parameters, platelet counts, and systemic signs to normal. Because some patients develop coagulopathy and thrombocytopenia that are resistant to antivenom treatment, some authors define control as clear improvement in hematologic parameters rather than complete normalization.

Because of the kinetic mismatch between venom and antivenom, recurrence occurs in 25–50% of patients with rattlesnake envenomation who receive CroFab. At the time of discharge, the patient should be informed of the possibility of recurrence and told to refrain from activities at high risk for trauma and to avoid any surgical procedures for 3 weeks. The patient should also receive in-

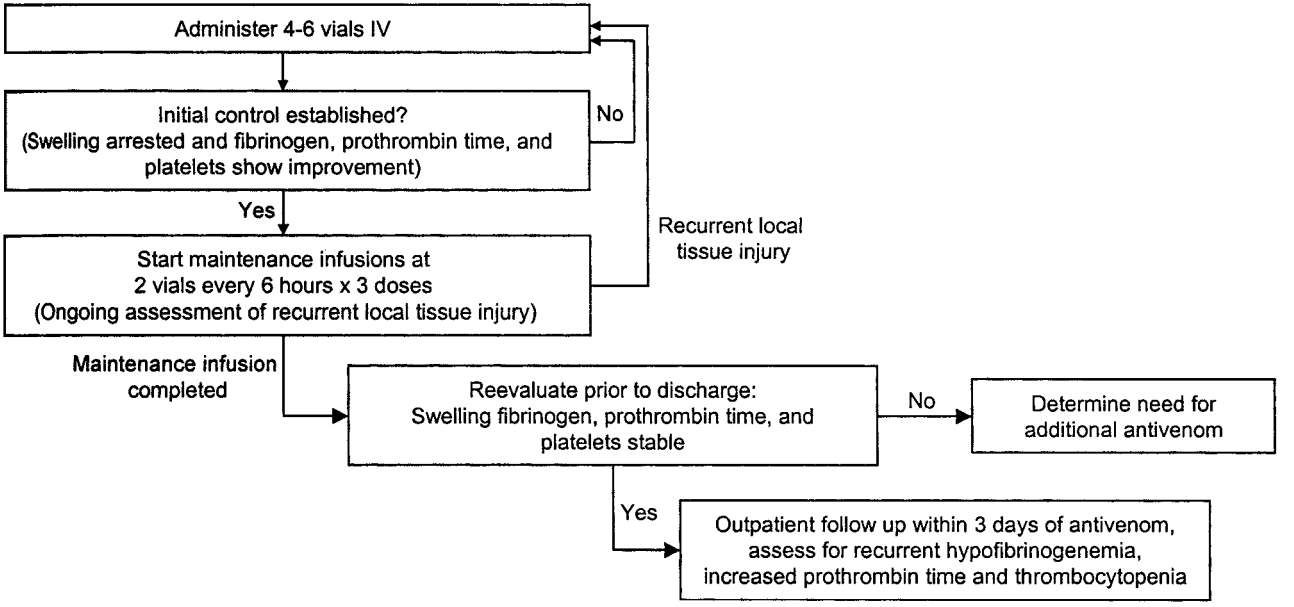

FIG. A33–1. Algorithm for crotaline polyvalent immune Fab antivenom administration for treatment of significant crotaline envenomation.

structions to watch for signs of bleeding, which may result from a coagulopathy or thrombocytopenia. All patients should have a followup prothrombin time, fibrinogen concentration, and platelet count obtained within 3–5 days of antivenom completion. Treatment recommendations for recurrent symptoms vary and there are no specific dosing regimens for retreatment. The only clear indication for retreatment is active bleeding, although we recommend application of clinical judgment for severe thrombocytopenia, coagulopathy, and patients at high risk for bleeding (such as Warfarin therapy). In the absence of any recurrent symptoms, patients should have regular telephone followup for 3 weeks to check for signs of serum sickness. If serum sickness develops, most patients respond to antihistamines and corticosteroids.

CROTALINE POLYVALENT ANTIVENOM (EQUINE ORIGIN)

Crotaline polyvalent antivenom (Antivenin Crotalidae Polyvalent, Wyeth-Ayerst) is a refined and concentrated preparation of equine whole immunoglobulins (IgG). It is a suspension of various venom-neutralizing antibodies prepared from the serum of horses hyperimmunized against the venom of four crotalines: the Eastern diamondback rattlesnake (*C. adamanteus*), the Western diamondback rattlesnake (*C. atrox*), the tropical rattlesnake (*C. durrisus terrificus*), and the fer-de-lance (*Bothrops atrox*). Even though it is not derived from copperheads or other crotalines, such as the Pacific rattlesnake, and timber rattlesnake, it is commonly administered following severe envenomation from these species and is effective because of venom cross reactivity. The antivenom is less effective against neurotoxicity resulting from the Mojave Desert rattlesnake envenomation.

Because it is a whole immunoglobulin product, this antivenom entails a significant incidence of immediate and delayed hypersensitivity reactions, including cutaneous hypersensitivity (urticaria), anaphylaxis, anaphylactoid reactions, and serum sickness. As the dose or rapidity of administration of antivenom is increased, the incidence of immediate and delayed hypersensitivity reactions also increases. There are few data on the exact incidence of allergic reactions, but some form of acute hypersensitivity has been reported to occur in nearly 25% of patients, and delayed serum sickness in 50% of patients receiving antivenom. More than 80% of patients develop serum sickness when more than 8 vials of antivenom are administered.

Technique of Administration

Before antivenom is administered, the patient should be asked about a history of asthma, atopy, current use of β-adrenergic antagonists, and previous horse serum-derived antivenom exposure. If any of these conditions are present, efforts should be made to obtain crotaline polyvalent immune Fab antivenom (CroFab). The use of skin testing for sensitivity to horse serum is controversial, and we do not recommend its use before antivenom administration. Both false-positive (approximately 50%) and false-negative (approximately 20%) skin tests are encountered.

The same overall procedure used in reconstitution of CroFab (above) can be used for the Wyeth product. The only major difference with regard to dosing Wyeth is that 10–20 vials are given as an initial dose and no maintenance doses are used. Repeat doses of 10 vials are given as needed to control coagulopathy, thrombocytopenia, and worsening tissue injury. On average, 30 vials are required for adequate treatment of severe rattlesnake envenomation. Followup should be organized as described above with the caveat that recurrent manifestations are rare.

ELAPID ANTIVENOM (EQUINE ORIGIN)

Antivenom of equine origin is available in limited supplies from Wyeth to treat envenomation by the Eastern coral snake (*Micrurus fulvius fulvius*) and Texas coral snake (*M. fulvius tenere*). Toxicity requiring treatment with antivenom has not been reported following bites from the less virulent Arizona (Sonoran, *Micruroides euryxanthus*) coral snake. In contrast to the recommendation to withhold crotaline polyvalent antivenom unless signs of significant envenomation are evident, coral snake antivenom is recommended prophylactically in any case where it is assumed or proven that the patient was bitten by a coral snake, regardless of symptoms. At least 3–5 vials of coral snake antivenom are given initially and repeated on the basis of the clinical condition. The caveats for the administration of crotaline antivenom (skin testing, rate of infusion, treatment of reactions) apply to coral snake antivenom, except that usually less antivenom is required for coral snakes.

118 Industrial Poisoning: Information and Control

TAKING AN OCCUPATIONAL HISTORY

The occupational health history should be a routine part of any medical history. The history should include several brief survey questions. Positive responses then lead to a more detailed occupational and environmental history, which is composed of three elements: present work, past work, and nonoccupational exposures.

The Brief Occupational Survey

The following three questions should be incorporated into the occupational survey:

- Exactly what kind of work do you do?
- Are you exposed to any physical (radiation, noise, extremes of temperature or pressure), chemical (liquids, fumes, vapors, dusts, or mists), or biologic hazards at work (Table 118–1)?
- Are your symptoms related in any way to starting or being away from work? For example, do they occur when you arrive at work at the beginning of the day or week, or when you work at a specific location, or during a specific process at work?

Present Work

Important data on a person's present job focuses on four areas: specifics of the job, hazardous exposures, health effects, and control measures (Table 118–2).

Specifics of the Job

It is insufficient simply to inquire what the patient does for a living. The patient should describe exactly what he or she does on any given day and for how long. Unusual and nonroutine tasks, such as those performed during overtime, maintenance, or in an emergency, should also be described.

Hazardous Exposures

The names and/or types of all chemicals or substances to which the patient may be exposed are important in determining potential adverse effects and any relationship to the patient's complaints. It is important to elicit any recent changes in suppliers of these products, as even a slight change in the formulation of a chemical may cause adverse effects in an individual who had no problems working with that compound previously. This information may be obtained from the material safety data sheet (MSDS), an important but not universally reliable source of information about the chemical. In addition to adverse health effects, the MSDS contains information on chemical reactivity, safety precautions, and other data.

TABLE 118–1. Hazard Classes, Hazard Types, and Several Common Examples Found in the Workplace

Hazard Class	Hazard Type	Examples
Physical	Man–machine interfaces	Repetitive motion Lifting Vibration Mechanical trauma, electric shock
	Physical environment	Temperature Pressure Long/rotating shifts
	Energy	Ionizing radiation: x-ray, ultraviolet Nonionizing radiation: infrared, microwave, magnetic fields Lasers Noise
Chemical	Solvents	Aliphatics, aromatics, alcohols, ketones, ethers, aldehydes, acetates, peroxides, halogenated compounds
	Metals	Lead, mercury, cadmium
	Gases	Combustion products, irritants, simple and chemical asphyxiants
	Dusts	Organic (wood) and inorganic (asbestos/silica)
	Pesticides	Organic chlorine, organic phosphorus, carbamate
	Epoxy resins and polymer systems	Toluene diisocyanate, phthalates
Biologic	Bacteria	*Bacillus anthracis, Legionella pneumophila, Borrelia burgdorferi*
	Viruses	Hepatitis, HIV, hantavirus
	Mycobacteria	*Mycobacterium tuberculosis*
	Rickettsia and *Chlamydia*	*Chlamydia psittaci, Coxiella brunetti*
	Fungi	*Histoplasma capsulatum, Coccidioides immitis*
	Parasites	*Echinococcus* spp, *Plasmodium* spp
	Envenomations	Arthropod, marine, snake
	Allergens	Enzymes, animals, dusts, insects, latex, pollen dusts

Health Effects

Table 118–3 highlights key items that support the diagnosis of work-related health effects.

Workplace Sampling, Monitoring, and Control

Control of workplace hazards begins with an industrial hygiene monitoring program. Employers are required to give results of both area and individual sampling to employees, but such programs are not universally present. It is important to determine whether the workplace employs any control measures, engineering controls, work practice protocols, administrative controls, and personal protective equipment. The existence of control measures usually indicates that the employer recognizes and has attempted to deal with a hazardous exposure.

TABLE 118–2. Components of an Occupational Health History

- Current work history
  - Specifics of the job
    - Employer's name
    - Type of industry
    - Duration of employment
    - Employment location, hours, and shift changes
    - Description of work process
    - Unusual activities of the job that are occasional (maintenance)
    - Adjacent work processes
  - Hazardous exposures (Table 118–1)
  - Possible health effects
    - Suspicious health problems
    - Temporality of symptoms
    - Specific distribution of symptoms (rash, paresthesias)
    - Affected coworkers
    - Presence or absence of known risk factors (smoking, alcohol)
  - Workplace sampling and monitoring
    - Individual and/or area air monitoring
    - Surface sampling
    - Biologic monitoring
    - Medical surveillance records
  - Exposure controls
    - Administrative controls
    - Process engineering controls
      - Enclosure
      - Shielding
      - Ventilation
      - Electrical and mechanically controlled interlocks
    - Personal protective equipment
      - Respirators
      - Protective clothing
      - Earplugs, glasses, gloves, face shields, head and foot protection
- Past work history
  - Review current work history for all past employment
- Nonoccupational exposures
  - Secondary employment
  - Hobbies
  - Outdoor activities
  - Residential exposures
  - Community contamination
  - Habits

Past Work

The occupational history should not be limited to the patient's current workplace and job. Many occupational diseases have long latency periods between exposure to a xenobiotic(s) and initial development of clinical symptoms.

Nonoccupational Exposures

Workers may be exposed to toxic substances in the course of pursuing secondary employment, hobbies, or outdoor activities in contaminated or industrial areas. Residential exposures, such as those from gas and wood stoves, chemically treated furniture and fabrics, and pest control, may also be relevant. It is

TABLE 118–3. Evidence Supporting Work-Relatedness of Occupational Disease

Known or documented exposure to a causative agent
Symptoms consistent with suspected workplace exposure
Suggested or diagnostic physical signs
Similar problems in coworkers or workers in related occupations
Temporal relationship of complaints related to work
Confirmatory environmental or biologic monitoring data
Scientific biologic plausibility
Absence of a nonoccupational etiology
Resistance to maximum medical treatment because employee continues to be exposed at work

important to ask patients about these potential exposures before focusing entirely on exposures in their primary place of employment.

EVALUATION AND CONTROL OF WORKPLACE HAZARDS

Initial Workplace Evaluation

The Occupational Safety and Health Act places legal responsibility for providing a safe and healthy workplace on the employer. The physician may wish to initiate a dialogue with a patient's employer to promote preventive action but should do so only with the patient's informed consent. Because the initial contact may influence subsequent events, it is important to identify an individual with an appropriate administrative role, such as someone in the company medical department, the patient's supervisor, the plant's safety officer, or the shop manager.

Industrial Hygiene Sampling and Monitoring

Equipment exists to measure airborne concentrations of toxic chemicals, noise levels, radiation levels, temperature, and humidity. Employees can be fitted with pumps and other devices to measure individual exposure levels at the breathing zone, where, depending on what controls are used, concentrations may vary from those in the general work area. These results can then be compared with the Occupational Safety and Health Act (OSHA) and other available standards to help determine the extent of the hazard and to formulate a control plan.

Control of Workplace Hazards

Workplace hazard control has traditionally relied on a hierarchy of methods to protect workers from exposure. The preferred solution is complete elimination of the hazard by *substitution.* Where this is not possible, controls that shield workers or reduce their exposure are the next preferred method. Finally, personal protective equipment, which requires a positive action from the worker, is the least-favored method.

Engineering Controls

Health and safety professionals prefer, and OSHA regulations require, where feasible, the use of engineering controls to reduce worker exposure to hazardous xenobiotics. Engineering controls include redesign or modification of

process or equipment to reduce hazardous emissions, isolation of a process through enclosure, automation of an operation, and installation of exhaust systems that remove hazardous dusts, fumes, and vapors.

Work Practices

Work practices are procedures that the worker can follow to limit exposure to hazardous xenobiotics. Examples are the use of high-powered vacuum cleaners instead of compressed air cleaning and pouring techniques that direct hazardous material away from the worker. Although not as effective as engineering controls, work practice can be a useful component of an overall hazard control program.

Administrative Controls

Administrative controls reduce the duration of exposure for any individual worker or reduce the total number of workers exposed to a hazard. Examples are rotation of workers into and out of hazardous areas and scheduling procedures likely to generate high levels of exposure, such as cleaning or maintenance activities, during nights or weekends.

Personal Protective Equipment

Personal protective equipment, such as respirators, earplugs, gloves, and hard hats, is the least effective but most commonly used control method. In some instances, the use of personal protective equipment may be unavoidable. An employer may need to control a hazardous exposure through a combination of measures, such as engineering controls and personal protective equipment.

Worker Education and Training

Regardless of the control measures employed, workers and supervisors need to be educated in the recognition and control of workplace hazards and the prevention of work-related illness and injury. The OSHA Hazard Communication Standard requires that employers train workers in ways to detect the presence or release of hazardous chemicals, their physical and health hazards, methods of protection against the hazards, and proper emergency procedures, as well as how to read the labeling system and how to read and use an MSDS.

Medical Monitoring

Together with worker education and industrial hygiene, a medical program can form the foundation of an effective occupational disease prevention regimen. *Medical screening* refers to the cross-sectional testing of a population of workers for evidence of excessive exposure or early stages of disease that may or may not be related to work and that may or may not influence the ability to tolerate or perform work. *Medical surveillance* refers to the ongoing evaluation, by means of periodic examinations, of high-risk individuals or potentially exposed workers to detect early pathophysiologic changes indicative of significant exposure.

INFORMATION RESOURCES

Healthcare professionals require information on industrial toxins in a number of situations, ranging from caring for an acutely ill patient in an emergency

department, when information must be obtained quickly, to caring for a patient with chronic symptoms that may reflect an occupational disease. The American College of Occupational and Environmental Medicine publishes a suggested reading list (*http://www.acoem.org*) that provides reference sources for information on toxicology, acute and chronic health effects, diagnosis, and treatment; assists in screening and surveillance; and provides information on groups at risk, product uses, and sources of further information. However, the use of these resources depends on the proper identification of the xenobiotic in question; if the xenobiotic, its generic name, and ingredients are not known, the research process becomes more difficult.

Other valuable information resources include regional poison control centers, employers and manufacturers, Chemical Transportation Emergency Center (CHEMTREC; 1-800-424-9300; *www.chemtrec.org*), Unions, Worker's Compensation Insurance Carriers, OSHA, National Institute for Occupational Safety and Health (NIOSH), US Environmental Protection Agency (EPA), National Toxicology Program (NTP) (*http://ntp-server.niehs.nih.gov*), and The Agency for Toxic Substances and Disease Registry (ATSDR) (*www.atsdr.cdc.gov*).

OBLIGATIONS OF THE HEALTHCARE PROVIDER TO THE INDIVIDUAL PATIENT, COWORKERS, EMPLOYER, GOVERNMENT, AND COMMUNITY

Occupational diseases and injuries are, in principle, preventable. Physicians who diagnose a work-related disease or injury have an opportunity, and an ethical obligation, to participate in the identification and control of workplace hazards and the prevention of further occupational illness and injury. Physicians can choose from a range of possible followup measures, the goals of which are to prevent recurrence or worsening of the disease or injury in the patient and to prevent the development of disease or injury in other potentially exposed workers. Some of these activities may necessitate contact with occupational medicine physicians, toxicologists, industrial hygienists, lawyers, journalists, government officials, management personnel, and union officials.

Obligations to the Patient

Inform the Patient That the Illness May Be Work-Related

When it is determined that the workplace is a factor in the etiology or aggravation of the patient's illness, this fact and its implications should be discussed with the patient.

Suggest How the Patient Can Reduce the Exposure

Adjustments in work habits that may be helpful may include using a respirator or other personal protective equipment provided by the employer, using workplace shower and dressing rooms to avoid carrying toxic chemicals from the workplace to the home, and avoiding ingestion of workplace toxins by careful handwashing before eating or smoking and by taking lunch, coffee, and smoking breaks away from the work station.

Suggest That the Patient Remove Himself or Herself from the Exposure

The employer may be willing to transfer the patient to a location away from the offending hazard. This may result in a reduction in pay, seniority, or other benefits, which may be compensable under Workers' Compensation. The em-

ployment provisions of the Americans with Disabilities Act (ADA) require employers to make "reasonable accommodations" for both work- and non–work-related disabilities.

Advise the Patient to Notify the Employer

Patients who are suffering from a work-related illness may be entitled to workers' compensation benefits, Social Security disability, or other government-sponsored benefit programs. Once a patient is informed that he or she has a work-related illness, strict time limits are set in motion, and failure to meet them can preclude the patient from successfully filing a claim or receiving needed benefits. The patient should be advised to provide written notice immediately to his or her employer of a work-related illness (supported by a physician's letter) and to seek advice about statutes of limitations and other requirements.

Obligations to Coworkers

A patient with a work-related illness should be advised to inform coworkers about his or her condition. If the patient belongs to a union, he or she should inform the union representative. If there is no union, the patient may contact OSHA or discuss the situation with the employer.

Obligation to Notify the Employer

When treating an occupational injury or illness, healthcare providers are often required to report to government agencies, health departments, or insurance carriers. As part of that reporting process, the employer should also be notified. When there is imminent danger to coworkers or the public health, the employer should also be contacted to correct the exposure situation.

Obligation to Notify the Government

States may have laws that require direct physician reporting of occupational disease. If management is uncooperative despite notification that a hazardous situation exists, OSHA should be contacted, with the patient's consent. Many states also require physicians to report any occupational injury or illness to the workers' compensation carrier.

Obligation to Inform Colleagues and the Public

It has happened that an individual primary care physician or specialist was the first to suspect a link between a workplace exposure and a serious health problem. Armed with an increased index of suspicion and the occupational history, the physician may be able to alert workers and companies and prevent the occurrence of a major health problem. Case reports in the medical literature, at medical meetings, or through the media can be very helpful in this regard.

119 Simple Asphyxiants and Pulmonary Irritants

The respiratory tract encounters nearly 3000 L of air during a typical 8-hour workday, and even mild exertion can triple the volume inhaled. The respiratory tract, as discussed in Chap. 22, performs several important physiologic functions. Its most important role involves the transfer of oxygen to hemoglobin across the pulmonary endothelium. Certain xenobiotics prevent adequate oxygenation of hemoglobin at the level of pulmonary gas exchange. Two mechanistically distinct groups of xenobiotics are capable of interfering with gas exchange: simple asphyxiants and pulmonary irritants. Impairment of transpulmonary oxygen diffusion, regardless of the etiology, reduces the oxygen content of the blood and can result in tissue hypoxia.

SIMPLE ASPHYXIANTS

Pathophysiology

Simple asphyxiants displace oxygen from ambient air, thereby reducing the fraction of oxygen in air, or FiO_2, below 21%, resulting in a fall of the partial pressure of oxygen. In general, simple asphyxiants have no pharmacologic activity. For this reason, exceedingly high ambient concentrations of these gases are necessary to produce asphyxia. Asphyxiation typically occurs in confined spaces or with extremely concentrated forms of the simple asphyxiants. The widespread use of liquefied gas, which expands several hundredfold on depressurization or warming, accounts for a substantial number of workplace injuries.

Clinical Manifestations

A patient exposed to any simple asphyxiant gas will develop characteristic symptoms of hypoxia (Table 119–1), which are directly related to the partial pressure of the gas in the air or, more correctly, to the reduction in ambient oxygen partial pressure.

Specific Xenobiotics

All noble gases, when compressed, form cryogenic liquids, which expand rapidly to their gas phase on decompression. The liberation of these gases in closed spaces may result in asphyxiation or freezing injuries. Xenon has unique anesthetic properties because of its high lipid solubility; the other noble gases have no direct toxicity.

Methane (CH_4) has no direct toxicity, and animals can breathe a mixture of 80% methane and 20% oxygen without manifesting hypoxic symptoms because their FiO_2, and thus their oxyhemoglobin saturation, is essentially normal. Methane, also known as natural gas and "swamp gas," may be present in high ambient concentrations in bogs of decaying organic matter. Because methane is odorless and undetectable without sophisticated equipment, natural gas is intentionally adulterated with a small concentration of ethyl mercaptan, a stenching agent, which is responsible for the well-recognized sulfur odor of natural gas. Ethane (C_2H_6) is an odorless gas with similar characteristics to methane that is occasionally implicated as a simple asphyxiant. It is also a com-

TABLE 119–1. Clinical Findings Associated with Reduction of Inspired Oxygen

FiO_2[a]	Signs/Symptoms
21	None
16–12	Tachypnea, hyperpnea, (resultant hypocapnia), tachycardia, reduced attention and alertness, euphoria, headache, mild incoordination
14–10	Altered judgment, incoordination, muscular fatigue, cyanosis
10–6	Nausea, vomiting, lethargy, air hunger, severe incoordination, coma
<6	Gasping respiration, seizure, coma, death

[a]At sea-level barometric pressure appropriate adjustments must be made for altitude and depth exposures.

ponent of natural gas and is used as a refrigerant. Propane (C_3H_8) is widely used in compressed, liquefied form both as an industrial and domestic fuel and as an industrial solvent. Butane (C_4H_{10}) is also a prevalent fuel and solvent.

Although not a simple asphyxiant gas by definition because it produces physiologic effects, carbon dioxide closely resembles simple asphyxiants from a toxicologic viewpoint. Dry ice, the frozen form of carbon dioxide, is an extremely cold substance (–141.3°F [–78.5°C]) that undergoes conversion from solid to gas without liquefaction, a process known as sublimation. Profound poisoning may occur when dry ice is allowed to sublimate in a closed space. Dissolved carbon dioxide, measured as the PCO_2, is primarily responsible for our respiratory drive. For this reason, exogenous carbon dioxide, combined with oxygen, was at one time used medically as a respiratory stimulant in neonates. Under normal conditions, ambient air contains approximately 0.03% CO_2. When ambient concentrations rise, uptake of carbon dioxide occurs, which stimulates respiration further, increasing the uptake of ambient carbon dioxide. Intense carbon dioxide exposure may produce rapid and lethal poisoning. However, unlike other simple asphyxiants, experimental models of acute carbon dioxide poisoning in which the PO_2 has been maintained at normal levels demonstrate that central nervous and respiratory systems manifestations occur within seconds. This suggests that CO_2 is not solely a simple asphyxiant but also possesses a potential for systemic effects.

Although nitrogen, like carbon dioxide, may produce clinical effects independently of hypoxemia, most poisonings are characterized by the manifestations of the simple asphyxiants. Poisoning by nitrogen gas is uncommon but may occur following the rapid evaporation of the liquid. Nitrogen poisoning, also known as nitrogen narcosis, occurs in underwater divers while breathing air, which contains 70% nitrogen. It has been called "rapture of the deep" (*l'ivresse des grandes profondeurs*) and has, unfortunately, led to many deaths in the subaquatic environment. The underlying mechanism of nitrogen narcosis is unknown, but the simple structure and relatively high lipophilicity of nitrogen suggest a mechanism similar to that of the anesthetic gases.

Treatment

Treatment for all patients poisoned by simple asphyxiants begins with immediate removal from exposure and ventilatory assistance. Provision of supplemental oxygen is preferable, but room air usually suffices; hyperbaric oxygen therapy is unnecessary. Restoration of oxygenation, through spontaneous or mechanical ventilation occurs after only several breaths. Support of vital functions is the mainstay of therapy but is generally unnecessary following a brief exposure.

PULMONARY IRRITANTS

The irritant gases are a heterogeneous group of chemicals that produce toxic effects via a final common pathway: the destruction of the integrity of the mucosal barrier of the respiratory tract (Table 119–2).

Pathophysiology

Irritant chemicals damage both the more prevalent type I pneumocytes and the surfactant-producing type II pneumocytes. Neutrophils recruited in response to inflammatory cytokines release toxic mediators that disrupt the integrity of the capillary endothelial cells. This host defense response results in accumulation of cellular debris and plasma exudate in the alveolar sacs, producing the characteristic clinical findings of acute lung injury (ALI). The specific mechanisms by which the irritant gases damage the pulmonary endothelial and epithelial cells vary and may include stimulation of cytokines, induction of free radicals or nascent oxygen, or the generation of acid–base reactions.

Clinical Manifestations

Regardless of the mechanism by which the mucosa is damaged, the clinical presentations of patients exposed to irritant gases are similar. Exposures to xenobiotics that result in irritation within seconds generally develop mucosal injury limited to the upper respiratory tract. Patients may present with oral, nasal, and pharyngeal pain in addition to drooling, mucosal edema, cough, or stridor. Conjunctival irritation or chemosis, as well as dermatologic irritation, is often noted. Agents that are less rapidly irritating may not provide an adequate signal of their presence and not prompt expeditious escape. Prolonged breathing thus allows entry of the toxic gas further into the bronchopulmonary system, where delayed toxic effects subsequently may be noted. Tracheobronchitis, bronchiolitis, bronchospasm, and ALI are typical inflammatory responses of this anatomic region and represent the spectrum of acute lower respiratory tract injury. ALI consists of the clinical, radiographic, and physiologic abnormalities caused by pulmonary inflammation and alveolar filling that must be both acute in onset and not attributable solely to pulmonary capillary hypertension as occurs in patients with congestive heart failure. The most severe manifestation of ALI is the acute respiratory distress syndrome (ARDS). Chapter 22 discusses the criteria for the diagnoses of ALI and ARDS. Typical radiographic abnormalities include bilateral pulmonary infiltrates with an alveolar filling pattern and a normal cardiac silhouette differentiating this syndrome from congestive heart failure.

Specific Xenobiotics

Acid- or Base-Forming Gases

Highly Water-Soluble Ammonia is a common industrial and household chemical used in the synthesis of plastics and explosives, as a fertilizer, a refrigerant, and a cleaning agent. The dissolution of NH_3 in water to form ammonium hydroxide (NH_4OH), a base, rapidly produces severe upper airway irritation.

Chloramines are a series of chlorinated nitrogenous compounds including monochloramine (NH_2Cl), dichloramine ($NHCl_2$), and trichloramine (NCl_3). The chloramines are most commonly generated by the admixture of ammonia

TABLE 119–2. Characteristics of Common Respiratory Irritants

Gas	Source/Exposure	Solubility (gm%)[a]	Detection Threshold (ppm)	Regulatory Standard (ppm)[b]	IDLH[c] (ppm)	STEL (ppm)
Ammonia	Fertilizer, refrigeration, synthetic fiber synthesis	90	5	50	300	35
Cadmium oxide fumes	Welding	I		0.005 mg/m^3	9 mg/m^3 (as Cd)	
Carbon dioxide	Exhaust, dry ice sublimation	0.2		5,000	40,000	30,000
Chloramine	Bleach plus ammonia					
Chlorine	Water disinfection, pulp and paper industry	0.7	0.3	0.5	10	1
Copper oxide fumes	Welding	I		0.1 mg/m^3	100 mg/m^3 (as Cu)	
Ethylene oxide	Sterilant	M		1	800	5
Formaldehyde	Chemical disinfection	M	0.8	0.016	20	2
Hydrogen chloride	Chemical	67	1–5	5	50	5
Hydrogen fluoride	Glass etching, semiconductor industry	M		3 (as F^-)	30 (as F^-)	6
Hydrogen sulfide	Petroleum industry, sewer, manure pits	0.4	0.025		100	50
Mercury vapor	Electrical equipment; thermometers; catalyst; dental fillings; metal extraction; heating or vacuuming elemental mercury	I		0.1 mg/m^3	10 mg/m^3	0.05
Methane	Natural heating gas, swamp gas		200			
Methyl bromide	Fumigant	2		20	250	
Nickel carbonyl	Nickel purification, nickel coating, catalyst	0.05		0.001	2 (as Ni)	
Nitrogen						
Nitrogen dioxide	Chemical synthesis; combustion emission		0.12	5	20	5
Nitrous oxide	Anesthetic gas, whipping cream dispensers (abuse), racing fuel additive			50		
Ozone	Disinfectant; produced by high-voltage electrical equipment	0.001	0.05	0.1	5	0.1

(continued)

TABLE 119–2. Characteristics of Common Respiratory Irritants *(continued)*

Gas	Source/Exposure	Solubility (gm%)[a]	Detection Threshold (ppm)	Regulatory Standard (ppm)[b]	IDLH[c] (ppm)	STEL (ppm)
Phosgene	Chemical synthesis; combustion of chlorinated compounds	sl	0.5	0.1	2	0.1
Phosphine	Fumigant; semiconductor industry	sl	2	0.3	50	1
Propane	Liquified propane gas		Odorless	1000	2100	
Sulfur dioxide	Environmental exhaust	23	1	2	100	5
Zinc chloride fumes	Artificial smoke (no longer in use)			1 mg/m^3	50 mg/m^3	2 mg/m^3
Zinc oxide	Welding		Odorless	5 mg/m^3	500 mg/m^3	10 mg/m^3

[a]gm% = grams of gas per 100 mL water; if applicable; I = insoluble; M = miscible; sl = slightly soluble.
[b]Standards are generally TLV-TWA, set by the ACGIH; some are PEL, set by OSHA.
[c]Immediately dangerous to life and health: NIOSH, Revised 1995 (documentation for each IDLH is available at http://www.cdc.gov/niosh/idlh/idlhintr.html).
STEL: NIOSH and OSHA 15 minute or ceiling.

with sodium hypochlorite (NaOCl) bleach, often in a misguided effort to potentiate their individual cleaning powers. On dissolution of the chloramines in the epithelial lining fluid, hypochlorous acid, ammonia, and oxygen radicals are generated, all of which act as irritants.

The largest and most important use of hydrogen chloride gas is in the production of hydrochloric acid. Dissolution of hydrogen chloride gas in lung water after inhalation similarly produces hydrochloric acid.

Hydrogen fluoride and its aqueous form, hydrofluoric acid, are used in the gasoline, glassware, building renovation, and semiconductor industries. Hydrogen fluoride gas dissolves in epithelial lining fluid to form a weak acid, hydrofluoric acid. Patients with inhalational exposure to hydrogen fluoride are not only at risk for local toxicity to the lungs and eyes, but systemic toxicity may also result. Frequent electrocardiographic evaluations for hyperkalemia, hypocalcemia, and hypomagnesemia are required. The administration of nebulized 2.5% calcium gluconate should be considered so as to limit both local toxicity and systemic fluoride absorption (made as 1.5 mL 10% calcium gluconate plus 4.5 mL 0.9% NaCl or sterile water). Systemic calcium salts should be administered as needed to correct hypocalcemia (Chap. 101 and Antidotes in Brief: Calcium).

Sulfur dioxide has multiple industrial applications and is a by-product found in smelting and oil refining. Sulfur dioxide is highly water soluble and has a characteristic pungent odor that provides warning of its presence at concentrations well below those that are irritating. In the presence of catalytic metals (Fe, Mn), environmental sulfur dioxide is readily converted to sulfurous acid (H_2SO_3) within water droplets. Sulfurous acid is a major environmental concern and the cause of "acid rain." Atmospheric sulfur dioxide and H_2SO_4 have severe health consequences; exposure results in a roughly dose-related bronchospasm, which is most pronounced and difficult to treat in asthmatic patients.

Intermediate Water Solubility Chlorine gas is a valuable oxidizing agent with varied industrial uses, and occupational exposure is common. Chlorine gas was used by both the French and the Germans in World War I as a chemical warfare agent (Chap. 126). Although chlorine gas is not generally available for use in the home, domestic exposure to chlorine gas is common. The admixture of an acid to bleach liberates chlorine gas. Concentrated chlorine gas can also be generated when aging swimming pool chlorination tablets, such as calcium hypochlorite [$Ca(OCl)_2$] or trichloro-*s*-triazinetrione (TST), decompose. The odor threshold for chlorine is low, but it may be difficult to distinguish toxic from permissible air concentrations until toxicity is manifest. The intermediate solubility characteristics of Cl_2 result in only mild initial symptoms following moderate exposure, and permit a substantial time delay, typically several hours, before the development of clinical symptoms. Chlorine dissolution in the lung water generates HCl and hypochlorous (HClO) acids. The hypochlorous acid rapidly decomposes into HCl and nascent oxygen (O^-). The unpaired nascent oxygen atom produces additional pulmonary damage by initiating a free-radical oxidative cascade.

Hydrogen sulfide exposures occur most frequently in the waste management, petroleum, and natural gas industries, although poisoning occurs in workers in the asphalt, synthetic rubber, and nylon industries, and, rarely, in hospital workers using acid to clean drains clogged with plaster of Paris sludge. Hydrogen sulfide inhibits mitochondrial respiration in a fashion similar to that of cyanide (Chap. 121).

H_2S has the distinctive odor of "rotten eggs," which, although helpful in diagnosis, is not specific for this gas. Despite a sensitive odor threshold of several parts per billion, rapid olfactory fatigue ensues, providing a misperception that the exposure and its attendant risk have diminished.

Poorly Water Soluble During World War I, phosgene was an important weapon of mass destruction that produced countless deaths (Chap. 126). Currently, phosgene is employed in the synthesis of various organic compounds, such as isocyanates, and it occasionally produces poisoning. Exposure to phosgene may initially produce limited manifestations but can result in acute mucosal irritation following intense exposure. In fact, the pleasant odor of fresh hay, rather than prompting escape, may ironically promote deep and prolonged breathing of the toxic gas. Delayed-onset acute lung injury (ALI) follows.

Oxidant Gases Oxygen toxicity is uncommon in the workplace but, ironically, is common in hospitalized patients. Although O_2 may produce central nervous system and retinal toxicity, pulmonary damage is more common. Humans can tolerate 100% O_2 at sea level for up to 48 hours without significant acute pulmonary damage. Acute lung injury and delayed pulmonary fibrosis result from prolonged exposures.

Oxides of nitrogen are a series of variably oxidized nitrogenous compounds. The most important substances included in this series are the stable free radicals nitrogen dioxide (NO_2), and nitric oxide (NO), as well as nitrogen tetroxide (dinitrogen tetroxide [N_2O_4]), nitrogen trioxide (N_2O_3), and nitrous oxide (N_2O). Nitrogen dioxide toxicity can occur when the propane-driven ice-cleaning machines are used in indoor ice-skating rinks with poor ventilation. Nitrogen dioxide is also the cause of "silo-filler's disease," in which the toxic gas is generated during the decomposition of silage. These various oxides of nitrogen may directly oxidize respiratory tract cellular membranes but more typically generate reactive nitrogen intermediates, or radicals, such as peroxynitrite ($ONOO^-$), which subsequently damage the pulmonary epithelial cells. In addition to generating oxidant cascades, dissolution in the respiratory tract water generates nitric acid and NO, which produce injury consistent with other inhaled acids.

Ozone is formed by the action of ultraviolet light on oxygen molecules and thus reduces the amount of solar ultraviolet irradiation reaching the earth. Ozone is another important component of photochemical smog and, as such, contributes to chronic lung disease. It is produced in significant quantities by welding and high-voltage electrical equipment and in more moderate doses by photocopying machines and laser printers. The pulmonary toxicity associated with ozone is primarily a result of its high reactivity toward unsaturated fatty acids and amino acids with sulfhydryl functional groups. Ozonation and free radical damage to the lipid component of the membrane initiates an inflammatory cascade, with resultant influx of inflammatory cells.

Miscellaneous Irritant Gases

Methylisocyanate (MIC) is one of a series of compounds sharing a similar isocyanate (N=C=O) moiety. Toluene diisocyanate (TDI) and diphenylmethane diisocyanate (MDI) are important chemicals in the polymer industry. In Bhopal, India, in 1984, an inadvertent release of MIC resulted in immediate and persistent respiratory symptoms in approximately 200,000 local inhabitants with approximately 2500 deaths. ALI was evident both clinically and radiographically.

Historically, riot control agents, or mace, consisted primarily of chloroacetophenone (CN) or chlorobenzylidenemalononitrile (CS). After low-level exposure, ocular discomfort and lacrimation alone are expected, accounting for their common appellation: "tear gas." The effects are transient, and complete recovery within 30 minutes is typical, although long-lasting pulmonary effects may occur (see Asthma and Reactive Airways Dysfunction Syndrome). Closed-space or close-range exposure, as well as physical exertion during exposure, may produce significant ocular toxicity, dermal burns, laryngospasm, ALI, or death. Because of their high potential for severe toxicity, CN and CS were replaced for civilian use by oleoresin capsicum, also known as pepper spray or pepper mace.

Acute inhalational exposures to certain metal compounds produce clinical effects identical to the chemical irritants. Zinc chloride ($ZnCl_2$), cadmium oxide (CdO), nickel carbonyl [$Ni(CO)_4$], and elemental mercury all produce pulmonary toxicity. Metal pneumonitis is distinguishable from other causes of ALI only by history or, retrospectively, by finding elevated serum or urine metal levels. In particular, metal pneumonitis should be differentiated from the more common and less consequential metal fume fever.

Management

Standard and Supportive Measures

Management of patients with acute respiratory tract injury begins with meticulous support of airway patency, by limiting bronchial and pulmonary secretions, and maintaining oxygenation. Supplemental oxygen, bronchodilators, and airway suctioning should be used if clinically indicated. Corticosteroid therapy, designed to reduce the inflammatory host-defense response, frequently improves surrogate markers of pulmonary damage such as oxygenation status but generally offers little outcome enhancement in patients with ARDS. Overall, there is little reason to suspect any specific benefit of corticosteroids and other antiinflammatory agents in most poisoned patients. However, because most studies demonstrate some benefit and little identifiable risk, corticosteroid use appropriately remains routine and based largely on local practices.

Prone ventilation, positive end-expiratory pressure (PEEP), and inverse-ratio ventilation are successful in enhancing the oxygenation of patients with ALI of various etiologies, but not necessarily successful in improving outcome. Lower-tidal-volume mechanical ventilation, using 6 mL/kg and plateau pressures of 30 cm of water, attenuated the inflammatory response and resulted in lower mortality and less need for mechanical ventilation than traditional volume ventilation with 12 mL/kg.

Neutralization Therapy

Case studies suggest that nebulized 2% sodium bicarbonate may be beneficial in patients poisoned by acid-forming irritant gases. The vast majority of these cases involve chlorine gas exposure, and most patients received other symptomatic therapies as well. Typically, 1 mL of 7.5% or 8.4% sodium bicarbonate solution is added to 3 mL of sterile water (resulting in an approximately 2% solution for nebulization). Because the administration of neutralizing acids for alkaline irritants, such as ammonia, has not been evaluated, they should not be used at this time.

Antioxidants

Antioxidants include reducing agents, such as ascorbic acid, *N*-acetylcysteine (NAC), free-radical scavengers, such as vitamin E, and enzymes, such as su-

peroxide dismutase. Although the concept of treating pulmonary oxidant stress with antioxidants or free-radical scavengers is intriguing, most currently available evidence suggests negligible benefit.

Advanced Pharmacologic Therapy

Perfluorocarbon Partial Liquid Ventilation Partial liquid ventilation involves the intrapulmonary administration of perfluorocarbons, which are inert liquids with low surface tension and excellent oxygen-carrying capacity. Studies in patients with non–chemically induced ARDS suggest that exfoliated tissue, and presumably persistent xenobiotic, may be effectively lavaged from the bronchopulmonary tree by this method. Perfluorocarbons improve oxygenation, and may have an antiinflammatory effect, as demonstrated by reduced oxidant lung injury following liquid ventilation in animals.

Exogenous Surfactant Although several experimental and clinical studies suggested the safety and efficacy of surfactant therapy in patients with ARDS, large randomized, controlled clinical trials fail to show a benefit on survival.

OTHER INHALATIONAL PULMONARY XENOBIOTICS

Inorganic Dust Exposure

A particulate, or dust, is a solid dispersed in a gas. Dust represents a substantial source of occupational particulate exposure and is an important cause of acute pulmonary toxic syndromes. A respirable particulate must have an appropriately small size (generally <10 μm) and aerodynamic properties to enter the terminal respiratory tree. Silicosis is a range of pulmonary diseases associated with inhalation of crystalline silica (SiO_2), or quartz. It typically occurs in workers involved in occupations where rock or granite is pulverized, including mining, quarry work, and sandblasting. Although usually a chronic disease, intense subacute exposure may produce acute silicosis in a few weeks and death within 2 years. Patients present with dyspnea, cor pulmonale, restrictive lung findings, and classic radiographic findings. Treatment is limited and includes steroids and supportive care.

Silicas combine with other minerals are referred to as silicates, the most important of which include asbestos and talc. Talc, or magnesium silicate [$(Mg_3Si_4)O_{10}(OH)_2$], is widely used in industry, but its home use has been curtailed over the past two decades because of cases of severe pulmonary injury.

Organic Dusts

Inhalation of dusts from cotton or similar natural fibers, usually during the refinement of cotton fibers (byssinosis), produces chest tightness, dyspnea, and fever that typically begin within 3–4 hours of exposure. Symptoms often resolve during the work week but return following a weekend hiatus.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, represents the final common pathway for many different organic dust exposures. The name attached to the individual syndrome identifies the associated occupation or substrate. For example, "bagassosis" is the term associated with sugar cane (bagasse), and "farmer's lung" is the term associated with moldy hay, although both are caused by thermophilic *Actinomycetes*. The implicated allergen is ca-

pable of depositing in the pulmonary parenchyma and eliciting a cell-mediated (type IV) immunologic response. The clinical findings include fever, chills, and dyspnea beginning 4–8 hours after exposure. The chest radiograph, although usually normal, may reveal diffuse or discrete infiltrates. Progressive disease is associated with a honeycombing pattern on the radiograph and a restrictive lung disease pattern on formal pulmonary function testing. Treatment includes corticosteroids and avoidance of the antigen.

Metal Fume Fever/Polymer Fume Fever

Metal fume fever is a recurrent influenzalike syndrome that develops several hours after exposure to metal oxide fumes generated during welding, galvanizing, or smelting. Although most symptoms of metal fume fever are similar to those expected with irritant gas exposures (dyspnea, cough, chest pain), the presence of fever, often between 100.4–102.2°F (38°–39°C), distinguishes the syndromes. Patients may also experience headache, metallic taste, myalgia, and chills. Direct pulmonary toxicity probably does not occur, and patients with metal fume fever generally have normal chest radiographs. However, as noted above, exposure to certain metal fumes, such as cadmium oxide and other zinc compounds, may produce direct toxic effects on the pulmonary parenchyma. The management of patients with metal fume fever is supportive and includes analgesics and antipyretics.

A remarkably similar syndrome occurs subsequent to inhaling pyrolysis products of fluorinated polymers (eg, Teflon), which is aptly termed "polymer fume fever."

ASTHMA AND REACTIVE AIRWAYS DYSFUNCTION SYNDROME

Asthma, or reactive airways disease, is a clinical syndrome that includes intermittent episodes of dyspnea, cough, chest pain or tightness, wheezes on auscultation, and measurable variations in expiratory airflow. Episodes are usually triggered by a xenobiotic or physical stimulus and resolve over several hours with appropriate therapy. The underlying process is immunologic in most cases, with allergen-triggered release of inflammatory mediators causing bronchiolar smooth muscle contraction and subsequent inflammation. Exposure to one of the 250 or more known sensitizers is usually associated with a latency period of weeks or months of exposure before symptom onset. Once symptoms begin, however, they recur consistently following reexposure to the inciting sensitizer. Treatment for exacerbations is comparable to standard asthma therapy and includes bronchodilators and corticosteroids. A change in workplace is often required to prevent permanent pulmonary dysfunction.

Acute exposure to irritant gas may result in the development of a persistent asthmalike syndrome that has also been termed reactive airways dysfunction syndrome (RADS), "irritant-induced asthma," or "occupational asthma without latency." Virtually every irritative xenobiotic is reported to cause this syndrome, and those not yet described are probably simply unrecognized. In comparison to patients with occupational asthma, patients with RADS have a lower incidence of atopy and are exposed to agents not typically considered to be immunologically sensitizing. Corticosteroids are the mainstay of therapy.

120 | Carbon Monoxide

HISTORY AND EPIDEMIOLOGY

Carbon monoxide (CO) is the leading cause of poisoning morbidity and mortality in the United States. In a given year, more than 2000 nonfire-related CO deaths occur, the majority of which are intentional. Carbon monoxide poisoning is also a contributor to the approximate 5613 smoke inhalation deaths each year. For the time period, 2001–2003, there were 15,200 patients treated annually in emergency departments for nonfatal, unintentional, nonfire-related CO exposure, of which more than half occurred in homes with faulty furnaces. Furthermore, delayed cognitive sequelae occur in up to 50% of patients with symptomatic acute poisoning.

Table 120–1 lists potential sources of CO that often result in unintentional poisoning.

CHEMISTRY

Carbon monoxide has a density of 0.968 relative to air. Carbon monoxide is readily absorbed after inhalation. The carboxyhemoglobin (COHb) concentration at equilibrium can be predicted from ambient concentrations as follows: COHb (%) = 100/[1 + (643/ppm CO)]. Once absorbed, CO is carried in the blood, primarily bound to hemoglobin. The Haldane ratio states that CO has approximately a 200–250 times greater affinity for oxygen than for hemoglobin. As a result, CO is primarily confined to the blood compartment, but eventually up to 15% of total CO body stores are taken up by tissue, primarily bound to myoglobin. Elimination of CO is dependent on oxygen tension. In volunteer studies, means of 249–320 minutes were reported on room air, which fell to 47–80 minutes with 100% oxygen.

Methylene chloride is metabolized in the liver to CO. Peak concentrations may not occur until 8 hours or longer after exposure.

PATHOPHYSIOLOGY

Carbon monoxide's most obvious effect is binding to hemoglobin, rendering it incapable of delivering oxygen to the cells. Thus even though the dissolved oxygen content (PO_2) is normal, the arterial oxygen content is significantly reduced (Chap. 22). Further insult occurs because CO causes a leftward shift of the oxyhemoglobin dissociation curve, thus decreasing the offloading of oxygen from hemoglobin to tissue. Carbon monoxide toxicity cannot be attributed solely to COHb-mediated hypoxia. The delivery of CO intracellularly and subsequent generation of carboxymyoglobin further impairs oxygen transport. Furthermore, evidence suggests a direct inhibitory effect of CO on cellular respiration by binding to mitochondrial cytochrome oxidase. Finally, a complex cascade of events results in delayed lipid peroxidation of the brain, which can be correlated with cognitive defects in animal models.

CLINICAL MANIFESTATIONS

Effects of Acute Exposure

The earliest symptoms associated with CO poisoning are often nonspecific and readily confused with other illnesses, typically a viral syndrome (Table 120–2). Because the typical presenting complaints include headache, dizzi-

TABLE 120–1. Sources of Carbon Monoxide Implicated in Poisonings

Anesthetic lime absorbents
Automobiles
Banked blood
Boats
Camp stoves and lanterns
Charcoal grills
Coffee roasting
Gasoline-powered equipment (eg, generators, power washers)
Ice resurfacing machines
Methylene chloride
Natural gas furnaces
Natural gas water heaters
Natural gas ranges and ovens
Propane-powered forklifts
Underground mine explosions
Wood pellet storage

ness, and nausea, and the most frequent exposures occur during winter, it is not surprising that influenza is the most common misdiagnosis. Continued exposure to CO can lead to symptoms attributable to oxygen-deficiency in the heart. Myocardial infarction, life-threatening dysrhythmias, and cardiac arrest are commonly described in victims of CO poisoning. In fact, acute mortality from CO is usually a result of ventricular dysrhythmias, probably predominantly caused by the accompanying cellular hypoxia.

The central nervous system is the most sensitive organ to CO poisoning. Acutely, otherwise healthy patients may manifest headache, dizziness, and ataxia at COHb concentrations as low as 15–20%; with longer exposures, syncope, seizures, or coma can result. Within a day of exposures that result in coma, the CT scan can show decreased density in the central white matter and globus pallidus (Fig. 120–1).

Metabolic acidosis with an elevated lactate accompanies tissue hypoxia. Cherry-red skin coloration occurs only after excessive exposure (2–3% of cases referred to one hyperbaric center) and may represent a combination of CO-induced vasodilation with concomitant tissue ischemia. Another classic but uncommon phenomenon is the development of cutaneous bullae following severe exposures.

Delayed Cognitive Effects

Most cases of delayed neurologic sequelae are associated with loss of consciousness in the acute phase of toxicity. Neurologic deterioration can be pre-

TABLE 120–2. Clinical Manifestations of Carbon Monoxide Poisoning

Headache	Vomiting
Nausea	Ataxia
Dizziness	Confusion
Weakness	Syncope
Chest pain	Dysrhythmias
Dyspnea	Myocardial ischemia
Vision blurred	Tachypnea

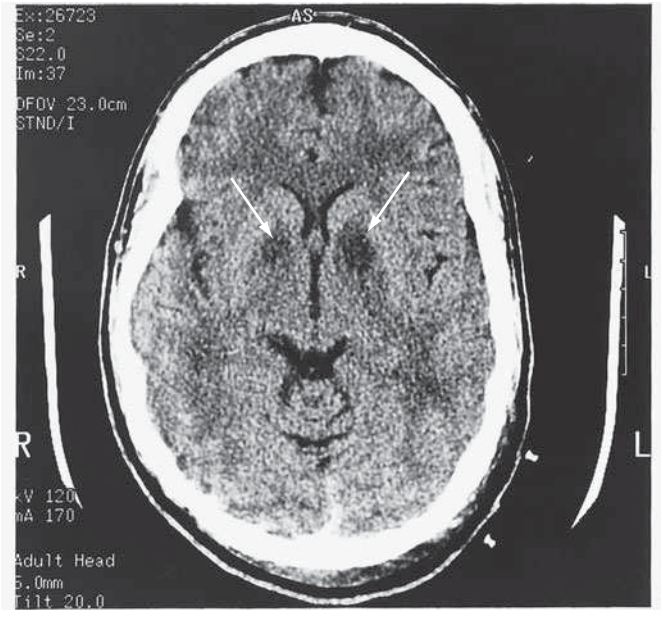

FIG. 120–1. Computerized tomography of the brain showing bilateral lesions of the globus pallidus (lucent areas) in a patient with poor recovery from severe carbon monoxide poisoning. (*Courtesy of New York City Poison Center Fellowship in Medical Toxicology.*)

ceded by a lucid period of 2–40 days after the initial CO poisoning and can include dementia, amnestic syndromes, psychosis, Parkinsonism, paralysis, chorea, cortical blindness, apraxia and agnosias, peripheral neuropathy, and incontinence. Patients older than age 30 years appear to be much more susceptible to developing delayed sequelae.

DIAGNOSTIC TESTING

The most useful diagnostic test obtainable in a suspected CO poisoning is a COHb concentration. Normal concentrations of COHb range from 0–5%. Concentrations at the high end of this range occur in neonates and patients with hemolytic anemia, because carbon monoxide is a natural by-product of the breakdown of protoporphyrin to bilirubin. Carboxyhemoglobin concentrations average 6% in 1-pack-per-day smokers, but can range as high as 10%. Although high COHb concentrations confirm exposure to CO, particular concentrations are not necessarily predictive of symptoms or outcome. Because of the similarities in extinction coefficients, COHb is misinterpreted as oxyhemoglobin on pulse oximetry (Chap. 20).

Additional laboratory tests may be useful in severe poisoning cases. An arterial or venous blood gas will confirm the presence of metabolic acidosis, as well as a high lactate, which may serve as a more reliable index of severity than COHb. Cardiac monitoring and a 12-lead ECG are essential to document ischemia or dysrhythmias in symptomatic patients with preexisting coronary ar-

tery disease or severe exposure. Mild elevations of creatine phosphokinase (CPK) are common (ranging from 20–1315 IU/L in one series of 65 cases), usually as a consequence of rhabdomyolysis rather than cardiac sources. However, CO can cause myocardial infarction, even in the presence of normal coronary arteries. Thus troponin concentrations may reflect diffuse cardiac myonecrosis rather than focal coronary artery disease.

Neuropsychological Testing

The extent of neurologic insult from CO can be assessed with a variety of tests. The most basic, is documentation of a normal neurologic examination with a quick mini-mental status examination. A more sensitive indicator of the acute effects of CO on cortical function is a detailed neuropsychological test battery developed specifically for CO patients. Although this battery is imperfect, it serves as the gold standard in many research studies.

Neuroimaging

Acute changes on computed tomography scan of the brain occur within 12 hours of the CO exposure that resulted in loss of consciousness. Symmetric low-density areas in the region of the globus pallidus, putamen, and caudate nuclei are frequently noted. Although a normal initial CT usually predicts a favorable outcome, changes in the globus pallidus and subcortical white matter early within the first day after poisoning are associated with poor outcomes. MRI appears to be superior in detecting basal ganglia lesions after CO poisoning. Regardless, neuroimaging usually does not influence patient management and can be reserved for patients who show poor response or have an equivocal diagnosis.

MANAGEMENT

The mainstay of treatment is initial attention to the airway. One hundred percent oxygen should be provided as soon as possible either by non-rebreather face mask or by endotracheal tube. The immediate effects of oxygen will be to increase the dissolved oxygen content of the blood and to enhance the dissociation of COHb. With oxygenation and intensive care treatment, hospital mortality rates for serious exposures range from 1–30%. Cardiac monitoring and intravenous access are necessary in any patient with systemic toxicity from CO poisoning. Hypotension can initially be treated with intravenous fluids; inotropes may also be necessary to treat myocardial depression. Standard advanced cardiac life support (ACLS) protocols can be followed for the treatment of life-threatening dysrhythmias. Patients with depressed mental status should have a rapid blood glucose determined.

Hyperbaric Oxygen

Hyperbaric oxygen (HBO) therapy appears to be the treatment of choice for patients with significant CO exposures. One hundred percent oxygen at ambient pressure reduces the half-life of COHb to approximately 40 minutes; at 2.5 atmospheres absolute (ATA), it is reduced to 20 minutes. Hyperbaric oxygen also increases the amount of dissolved oxygen by about 10-fold, which alone is sufficient to supply metabolic needs. Hyperbaric oxygen is more than just a modality to clear COHb more quickly than ambient oxygen. More importantly, hyperbaric, but not normobaric, oxygen therapy prevents brain lipid peroxida-

tion in animals. Clinical studies of the effectiveness of HBO in preventing neurologic damage from CO are not as convincing as basic science studies suggest. Despite this, the preponderance of evidence suggests a benefit of HBO, with little inherent risk (see Antidotes in Brief: Hyperbaric Oxygen).

Indications for Hyperbaric Oxygen Therapy

Although specific indications for HBO after acute CO poisoning are listed in Table 120–3, these have not been prospectively evaluated. The patients most likely to benefit are those most at risk for persistent or delayed neurologic sequelae, such as those presenting in coma. Another potential marker for delayed neurologic sequelae is a history of syncope. Patients with long exposures, or "soaking" periods, are also at greater risk for neurologic sequelae. The presence of a significant metabolic acidosis may be a surrogate marker for this. In a recent prospective clinical trial of CO poisoning, the incidence of cerebellar dysfunction portended a higher incidence of cognitive sequelae. Therefore, difficulty with finger-to-nose, heel-to-shin, rapid alternating hand movements, and ataxia should be considered indications for HBO. Patients with other mild neurologic findings, for example, headache, warrant at least several hours of 100% oxygen by non-rebreather face mask until symptoms resolve. If symptoms do not resolve, HBO can be considered; however, any delay in HBO may decrease its efficacy.

Delayed Administration of Hyperbaric Oxygen

The optimal timing of HBO treatments for CO poisoning is unclear. Patients treated later than 6 hours after exposure tend to have worse outcomes in terms of delayed sequelae and mortality (30% vs. 14%). Meanwhile, HBO treatments delivered within 6 hours after CO poisoning in patients with loss of consciousness seem to be almost completely preventive of neurologic sequelae. However, patients may benefit if treated even later. In the most recent randomized clinical trial showing beneficial effects of HBO, although all patients were treated within 24 hours of exposure, 38% of patients were treated later than 6 hours. Thus, it is reasonable to consider HBO within 24 hours of presentation for symptomatic acute poisoning.

Repeat Treatment with Hyperbaric Oxygen

Although a recent randomized clinical trial demonstrated that three HBO treatments within the first 24 hours improved cognitive outcome, no group was treated with only one or two HBO sessions. Regardless, multiple treatments are advocated by some authors for patients who have persistent symptoms, particularly coma, that do not clear after the first HBO session. How-

TABLE 120–3. Suggested Indications for Hyperbaric Oxygen

Syncope
Coma
Seizure
Altered mental status or confusion
Carboxyhemoglobin >25%
Abnormal cerebellar examination
Fetal distress in pregnancy

ever, because prospective studies comparing single versus multiple courses of HBO therapy have failed to confirm any benefit from repeated HBO treatment, routine use of multiple treatments cannot be recommended at this time.

Treatment of Pregnant Patients

The management of CO exposure in the pregnant patient is difficult because of the potential adverse effects of both the toxin and its treatment. A literature review of all CO exposures during pregnancy revealed a high incidence of fetal central nervous system damage and stillbirth after severe maternal poisonings. Based on animal studies, it was traditionally thought that fetal hemoglobin had a high affinity for CO. However, such data may not apply to humans because in vitro work shows that human fetal hemoglobin actually has less affinity for CO than maternal hemoglobin, at a ratio of 0.8. The more important issue with maternal CO exposure is the precipitous drop in fetal arterial oxygen content that occurs within minutes. It is the ensuing hypoxia of the fetus, rather than the increase in fetal COHb, that is of concern.

Because maternal COHb does not necessarily predict fetal demise, clinicians must direct their attention to maternal symptoms of CO toxicity. Multiple case series demonstrate that pregnant women who present with normal mental status and no loss of consciousness have excellent outcomes in terms of normal deliveries.

The bigger dilemma for the clinician is the approach to treatment of seriously symptomatic, CO-poisoned, pregnant patients. All patients should receive 100% oxygen by face mask, at least until the mother is asymptomatic. Some authors recommend longer oxygen therapy. Extensive human experience suggests that HBO is safe in pregnancy. There currently is no scientific validation for an absolute concentration at which to provide HBO therapy for a pregnant patient after CO exposure. When the mother meets the above criteria based on symptoms, HBO seems warranted. In addition, most suggest a lower absolute concentration based on the relative hypoxia of the fetus. Additional criteria include any signs of fetal distress, such as abnormal fetal heart rate.

Hyperbaric Oxygen

During hyperbaric oxygen (HBO) therapy, an individual breathes 100% O_2 while exposed to increased atmospheric pressure. Treatments are carried out in either a monoplace (single patient) or multiplace (typically 2–14 patients) chamber. Pressures applied while in the chamber are usually 2–3 atmospheres absolute (ATA), and treatments typically are for 2–8 hours, depending on the indication. During treatment, the arterial oxygen tension (PO_2) typically exceeds 2000 mm Hg. HBO should be viewed as a drug and the hyperbaric chamber as a dosing device.

In the context of an antidote, HBO is most commonly used for treatment of carbon monoxide (CO) poisoning. There is also a limited experience using HBO for life-threatening poisonings from cyanide (CN), hydrogen sulfide (H_2S), and carbon tetrachloride (CCl_4), and in patients with high methemoglobin levels unresponsive to methylene blue.

CARBON MONOXIDE

Therapeutic mechanisms of action for HBO are based on elevation of both the hydrostatic pressure and the partial pressure of oxygen. Elevation of the hydrostatic pressure causes a reduction in the volume of gas. This action has direct relevance to pathologic conditions where gas bubbles are present in the body, such as arterial gas embolism and decompression sickness. Because, under normal environmental conditions, hemoglobin is virtually saturated with oxygen on passage through the pulmonary microvasculature, the primary effect of HBO is to increase dissolved oxygen content of plasma. Application of each additional atmosphere of oxygen increases the dissolved oxygen concentration in the plasma by 2.2 mL O_2/dL (vol %) (Chap. 22).

Humans exposed to 100% O_2 versus air have approximately 38% more nitric oxide (·NO) in their exhaled breath. This intracellular production of ·NO appears to be the basis for the inhibitory effect of HBO on neutrophil adhesion. Exposure to 2.8–3.0 ATA O_2 for 45 minutes temporarily inhibits neutrophil adherence mediated by the activation-dependent β_2 integrins on the neutrophil membrane. The ability of HBO to inhibit the function of neutrophil β_2 integrins ameliorates reperfusion injuries of brain, skeletal muscle, and intestine, as well as smoke-induced lung injury, decompression sickness, and encephalopathy caused by CO poisoning.

Administration of supplemental oxygen is the cornerstone of treatment for CO poisoning. Oxygen inhalation will hasten the dissociation of CO from hemoglobin and provide enhanced tissue oxygenation. HBO causes carboxyhemoglobin (COHb) dissociation to occur at a rate greater than that achievable by breathing pure O_2 at sea-level pressure. Additionally, HBO accelerates restoration of mitochondrial oxidative processes.

Delayed neurologic sequelae are the common form of CO-mediated morbidity. Between 23–46% of patients with CO poisoning develop impairments of concentration and learning, dementia, cog wheel rigidity, amnesia, and/or depression between 6 days and 7 weeks after poisoning. Different neuroimaging techniques on CO victims have found acute vascular abnormalities and atypical coupling between cerebral blood flow and neuronal O_2 demand. These changes precipitate neutrophil adherence, and activated neutrophils

initiate a cascade of events that ultimately causes delayed neurologic dysfunction (Fig. A34–1).

HBO inhibits this cascade. Animals poisoned with CO and treated with HBO have a more rapid improvement in cardiovascular status, lower mortality, and lower incidence of neurologic sequelae.

Supporting Clinical Data

Although animal data are highly supportive of HBO therapy, human studies assessing efficacy of HBO for acute CO poisoning offer somewhat conflicting results. While many of the negative studies suffer from significant methodologic flaws, the positive studies are also highly criticized. Thus HBO treatment for acute CO poisoning rests on a solid scientific rationale and basic science research with some supportive randomized controlled clinical trials.

The optimal dose of HBO, number of treatments and treatment pressure, and the time after which it is no longer an effective therapy are not yet clearly defined. Randomized trials have treated patients as soon as possible after CO poisoning based on work suggesting that there is a 6 hour window of greatest opportunity. Yet it is possible that the time of potential benefit goes beyond what has been investigated for some patients. The requisite number of treatments also remains unclear. Chapter 120, and specifically Table 120–3, reviews the clinical indications for HBO in CO poisoning in greater detail.

METHYLENE CHLORIDE

Methylene chloride (CH_2Cl_2) is an organic solvent used commercially in aerosol sprays, as a solvent in plastics manufacturing, photographic film production, and food processing, as a degreaser, and as a paint stripper. It is readily absorbed through the skin or by inhalation and metabolized by the cytochrome P450 oxidase system to yield CO. This process is slow, and peak COHb concentrations of 10–50% may not be reached for 8 hours or more. Methylene chloride toxicity can have many of the same acute manifestations as CO poisoning. Acute signs and symptoms are attributable to the direct effects of this solvent on the central nervous system and to concomitant hypoxia. Treatment with HBO in this setting has been reportedly successful.

COMBINED CARBON MONOXIDE AND CYANIDE

CO and CN poisonings can occur together in victims of smoke inhalation. Experimental evidence suggests that these agents can produce synergistic toxicity. Animal studies demonstrate that ambient-pressure 100% O_2 can enhance protection from CN toxicity. Hyperbaric oxygen may have direct effects to reduce CN toxicity or to augment antidote treatments. In a series of smoke inhalation victims with both toxic CO and CN concentrations who received both HBO and treatment for CN involving sodium nitrite and sodium thiosulfate, 4 of 5 patients survived without apparent neurologic damage.

HYDROGEN SULFIDE

H_2S binds to cytochrome aa_3 and impairs oxidative phosphorylation. Hence, one of its mechanisms of toxicity is similar to that of CN, although it is more readily dissociated from cytochrome oxidase by O_2. In animals, HBO may be more effective than sodium nitrite in preventing mortality. Relatively late treat-

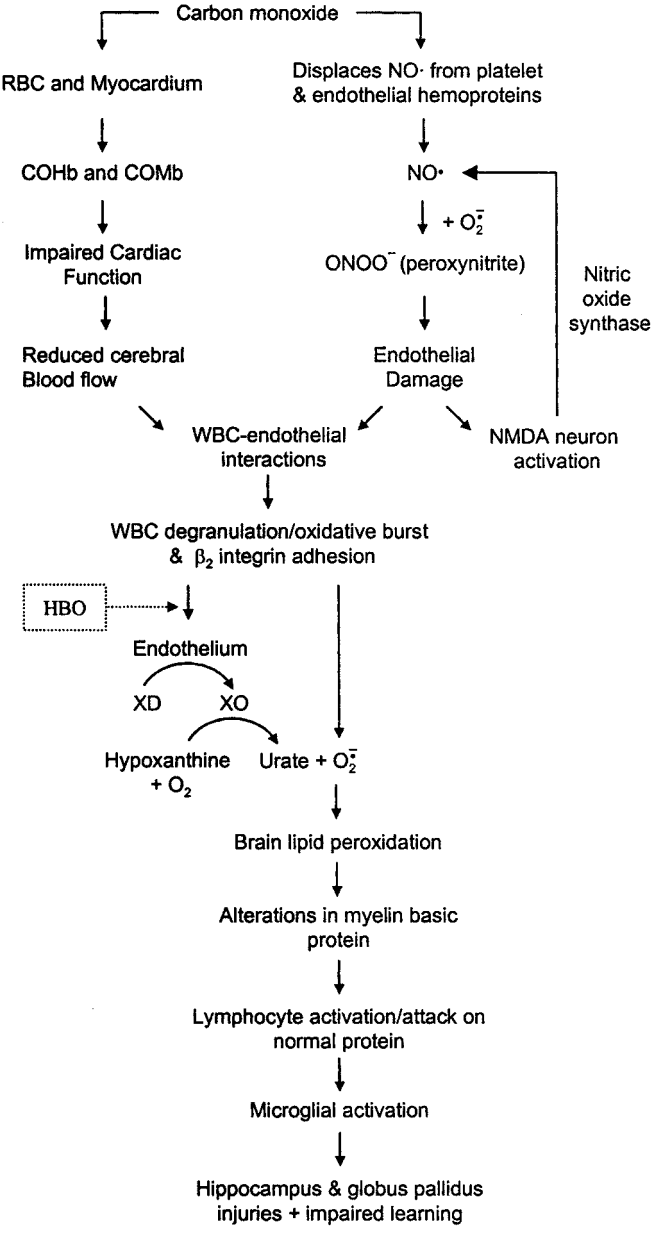

FIG. A34–1. Cascade of events as identified in rat model of carbon monoxide poisoning. COHb = carboxyhemoglobin; COMb = carboxymyoglobin; HBO = hyperbaric oxygen; NMDA = *N*-methyl-D-aspartate; NO· = free radical nitric oxide; RBC = red blood cell; WBC = white blood cell; XD = xanthine dehydrogenase; XO = xanthine oxidase.

ment with HBO, 10 hours or more after poisoning, is reported to be beneficial in some, but not all, cases. Thus while there is no definitive data regarding use of HBO in H_2S poisoning, it should be considered in refractory cases.

CARBON TETRACHLORIDE

In animals, CCl_4-induced hepatotoxicity is diminished by HBO therapy. Additionally, there are several case reports of patients surviving potentially lethal ingestions with HBO therapy. HBO appears to inhibit the mixed-function oxidase system responsible for conversion of CCl_4 to hepatotoxic free radicals.

GENERAL PATIENT MANAGEMENT

Hyperbaric treatment centers typically have the ability to manage patients who require critical care support. Plans for treatment begin while the patient is still in the emergency department, before transport to the hyperbaric chamber is initiated. Issues to be addressed include informed consent; determination that all intravenous/arterial lines and nasogastric tubes/Foley catheters are secured; capping all unnecessary intravenous catheters; placing chest tubes to one-way Heimlich valves; replacing air in endotracheal tube cuffs with water to avoid excessive air leakage at pressure; and adequately sedating or paralyzing the patient as clinically indicated. There is a substantial clinical experience demonstrating that patients can be transported without adverse events. Preexisting conditions that require evaluation for possible management before HBO is initiated include claustrophobia, sinus congestion, and patients with scarred or noncompliant structures in the middle ear such as otosclerosis.

Middle-ear barotrauma is the most common adverse effect of HBO treatment. As the ambient pressure within the hyperbaric chamber is increased, a patient must be able to equalize the pressure within the middle ear by autoinsufflation. When autoinsufflation fails, tympanostomy tubes must be placed. One series reported the incidence of tube placement as approximately 4%. Biochemical toxicity caused by O_2 can be manifested by injuries to CNS, lungs, and eyes. CNS O_2 toxicity is manifested as a seizure. Since in any environment with an elevated concentration of O_2 there is a fire hazard, and scrupulous attention must be devoted to avoiding an ignition source.

121 Cyanide and Hydrogen Sulfide

CYANIDE POISONING

History and Epidemiology

In 1782, a Swedish chemist isolated hydrogen cyanide. He reportedly died in 1786 from cyanide poisoning. Napoleon III was the first to employ hydrogen cyanide as a chemical warfare agent. In World War I, hydrogen cyanide was used on the battlefield; during World War II, it was used as a genocidal agent (Zyklon B) by the Nazis.

The majority of reported cyanide exposures are unintentional. These events frequently involve chemists or technicians working in laboratories where cyanide salts are common reagents. Cyanide poisoning may also result from smoke inhalation, as the combustion of wool, silk, synthetic rubber, and polyurethane releases cyanide.

Suicidal and homicidal cyanide poisonings produce mass fatalities. Potassium cyanide was used in the 1978 Jonestown mass suicide in which more than 900 people died. Seven deaths resulted from consumption of cyanide-tainted acetaminophen in 1982.

Ingestion of cyanogenic chemicals (ie, acetonitrile, acrylonitrile, and propionitrile) is another source of cyanide poisoning. Acetonitrile (C_2H_3N) and acrylonitrile (C_3H_3N) are themselves nontoxic, but biotransformation liberates cyanide. Many plants contain cyanogenic glycosides (Chap. 114). Finally, iatrogenic cyanide poisoning may occur during the use of nitroprusside as a vasodilator to reduce blood pressure and afterload. Each nitroprusside molecule contains five cyanide molecules, which are slowly released.

Pharmacology, Pharmacokinetics, and Toxicokinetics

Acute toxicity occurs through a variety of routes, including inhalation, ingestion, dermal, and parenteral. The dose of cyanide required to produce toxicity is dependent on the form of cyanide (gas or salt), the duration, and the route of exposure. An adult oral lethal dose of potassium cyanide (KCN) is approximately 200 mg. An airborne concentration of 270 ppm [μg/mL] of hydrogen cyanide (HCN) may be immediately fatal, and exposures greater than 110 ppm for longer than 30 minutes are generally considered life-threatening.

The major route for detoxification of cyanide is the enzymatic conversion to thiocyanate. Two sulfur transferase enzymes—rhodanese (thiosulfate-cyanide sulfurtransferase) and β-mercaptopyruvate-cyanide sulfurtransferase—catalyze this reaction. Thiocyanate has relatively little inherent toxicity and is eliminated in urine. A number of minor pathways of metabolism (less than 15% of total) account for cyanide elimination, including conversion to 2-aminothiazoline-4-carboxylic acid, incorporation into the 1 carbon metabolic pool, or in combination with hydroxocobalamin to form cyanocobalamin.

Pathophysiology

Cyanide is an inhibitor of multiple enzymes, including succinic acid dehydrogenase, superoxide dismutase, carbonic anhydrase, and cytochrome oxidase. Cytochrome oxidase is essential for oxidative phosphorylation and, hence, aer-

obic energy production. It functions in the electron transport chain within mitochondria, converting catabolic products of glucose into adenosine triphosphate (ATP). Cyanide induces cellular hypoxia by inhibiting cytochrome oxidase at the cytochrome a_3 portion of the electron transport chain (Fig. 121–1). Lactic acidemia occurs because of failure of aerobic energy metabolism.

Cyanide is also a potent neurotoxin that exhibits a particular affinity for regions of the brain with high metabolic activity and for regions with a high affinity to cyanide. Central nervous system injury occurs via several mechanisms, including impaired oxygen use, oxidant stress, and enhanced release of excitatory neurotransmitters. Cyanide enhances *N*-methyl-D-aspartate (NMDA) receptor activity and directly activates the NMDA receptor, which stimulates Ca^{2+} entry leading to cell death.

Clinical Manifestations

Acute Exposure to Cyanide

There is no reliable pathognomonic symptom or toxic syndrome associated with acute cyanide poisoning. Clinical manifestations reflect rapid dysfunction of oxygen-sensitive organs, with central nervous and cardiovascular findings predominating. The time to onset of symptoms is typically seconds with inhalation of gaseous HCN or intravenous injection of a water-soluble cyanide salt, and several minutes following the ingestion of an inorganic cyanide salt. The clinical effects of cyanogenic chemicals are often delayed and the time course varies (range: 3–24 hours) depending on the rate of biotransformation.

Central nervous system signs and symptoms are typical of progressive hypoxia and include headache, anxiety, agitation, confusion, lethargy, seizures, and coma. A centrally mediated tachypnea occurs initially, followed by bradypnea. The cardiovascular responses to cyanide include an initial period of bradycardia and hypertension, followed by hypotension with reflex tachycardia, but the terminal event is consistently bradycardia and hypotension. Both cardiogenic pulmonary edema and acute lung injury are found at autopsy.

Gastrointestinal toxicity may occur following ingestion of inorganic cyanide and cyanogens and include abdominal pain, nausea, and vomiting.

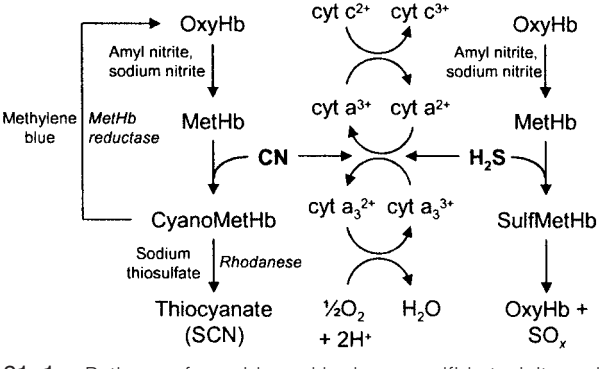

FIG. 121–1. Pathway of cyanide and hydrogen sulfide toxicity and detoxification.

These symptoms are caused by hemorrhagic gastritis secondary to the corrosive nature of cyanide salts. Cutaneous manifestations may vary. Traditionally, a cherry-red skin color is described as a result of increased venous hemoglobin oxygen saturation due to the inability to use oxygen at the tissue level. Despite the inference in the name, cyanide does not directly cause cyanosis.

Delayed Clinical Manifestations of Acute Exposure

Survivors of serious, acute poisoning may develop delayed neurologic sequelae characteristic of Parkinson disease (dystonia, dysarthria, rigidity, and bradykinesia). Symptoms typically develop over weeks to months, but subtle findings can be present within a few days. Cranial CT and MRI consistently reveal basal ganglia (globus pallidus, putamen, and hippocampus) damage.

Chronic Exposure to Cyanide

Chronic exposure to cyanide results in insidious syndromes, including tobacco amblyopia, tropical ataxic neuropathy, and Leber hereditary neuropathy. Chronic exposure is also associated with thyroid disorders such as hypothyroidism and goiters, because thiocyanate is a competitive inhibitor of iodide entry into the thyroid.

Diagnostic Testing

Because of nonspecific symptoms and delay in laboratory cyanide confirmation, the clinician must rely on historical circumstances and some initial findings to raise suspicion of cyanide poisoning and institute therapy. Laboratory findings suggestive of cyanide poisoning include metabolic acidosis, elevated lactate, and increased anion gap. Elevated venous oxygen saturation (usually above 90%) results from reduced tissue extraction. In a small group of patients in whom the diagnosis of cyanide poisoning was strongly suspected clinically, a plasma lactate concentration of greater than 8 mmol/L was associated with a sensitivity of 94%, a specificity of 70%, a positive predictive value of 64%, and a negative predictive value of 98% for a blood–cyanide concentration of greater than 1.0 μg/mL.

Blood cyanide determination can confirm toxicity, but this determination is not available in a sufficiently rapid manner to affect initial treatment. Whole blood or serum is usually analyzed. Whole-blood concentrations are twice serum concentrations because of the sequestration of cyanide in red blood cells. Background whole-blood concentrations in nonsmokers range between 0.02–0.5 μg/mL. Coma and respiratory depression is associated with concentrations greater than 2.5 μg/mL and death with levels greater than 3 μg/mL.

Management

Care begins by directing attention to airway patency, ventilatory support, and oxygenation. Intravenous access should be rapidly obtained and blood samples sent for renal function, glucose, and electrolyte determinations. Next, 100% oxygen should be supplied, followed as rapidly as possible by the cyanide antidote kit, which contains both nitrites and thiosulfate and or hydroxocobalamin. Each component has efficacy when given alone in animal models

of cyanide poisoning, but even greater benefit is achieved when their use is combined (see Antidotes in Brief: Sodium and Amyl Nitrites; Antidotes in Brief: Sodium Thiosulfate; and Antidotes in Brief: Hydroxocobalamin). Acidemia should be treated with adequate ventilation and sodium bicarbonate administration. Initiation of crystalloid and a vasopressor infusion for hypotension is warranted.

Instillation of activated charcoal is often considered ineffective because of low binding of cyanide (1 g activated charcoal adsorbs 35 mg cyanide). However, a potentially lethal oral dose of cyanide, a few hundred milligrams, is within the adsorptive capacity of a 1 g/kg dose of activated charcoal. Based on the potential benefits and minimal risks, activated charcoal should be considered in the patient with an intact secured airway.

Patients who do not survive cyanide poisoning are suitable organ donors. Heart, liver, kidney, pancreas, cornea, skin, and bone have been successfully transplanted following cyanide poisoning.

HYDROGEN SULFIDE POISONING

History and Epidemiology

Hydrogen sulfide is produced by bacterial decomposition of proteins and industrial activities such as pulp paper mills, petroleum distillation and refining, roofing asphalt tanks, and coke manufacturing from coal. It is a major industrial hazard in oil and gas production, particularly in sour gas fields (natural gas containing sulfur). Decay of sulfur-containing products, such as fish, sewage, and manure, also produces hydrogen sulfide.

Hydrogen sulfide (H_2S) toxicity is uncommon. The U.S. Occupational Safety and Health Administration (OSHA) records show 80 occupational fatalities between 1984 and 1994. Between 1990 and 1999, hydrogen sulfide poisoning was associated with the deaths of 18% of US construction workers killed by toxic inhalation. Many died while working in confined spaces. Numerous case reports include would-be rescuers, who themselves became victims when they attempted a rescue in an environment with high concentrations of hydrogen sulfide with inadequate personal protective equipment.

Hydrogen sulfide is also implicated in environmental disasters. In 2003, a gas drilling incident in southwest China released natural gas and a cloud of hydrogen sulfide into a populated mountainous area. More than 200 people died, 9000 were treated for injuries, and more than 40,000 were evacuated.

Pharmacology

Hydrogen sulfide is a colorless gas, more dense than air, with an irritating odor of "rotten eggs." It is highly lipid soluble, a property that allows easy penetration of biologic membranes. Absorption usually occurs through inhalation, and it is rapidly distributed to tissues.

Hydrogen sulfide produces intense irritation. It reacts with the moisture on the surface of mucous membranes to form sodium sulfide, which produces an irritant chemical effect on the eyes and nose. Despite skin irritation, it has little dermal absorption.

Systemic toxicity results from inhibition of cytochrome a_3 oxidase with even a higher affinity than cyanide (Fig. 121–1). The resulting syndrome is

essentially identical to cyanide with one exception: hydrogen sulfide binding is spontaneously reversible. In addition to cytochrome inhibition, H_2S opens the mitochondrial permeability transition pore, generating reactive oxygen species and compromising glycolysis.

Toxicokinetics

The major pathways of hydrogen sulfide detoxification are enzymatic and nonenzymatic oxidation of sulfides and sulfur to thiosulfate and polysulfides. It is also detoxified when it binds to methemoglobin to form sulfmethemoglobin. Sulfhemoglobin is not found in significant concentrations in the blood of animals or fatally poisoned humans.

Clinical Manifestations

Acute Manifestations

Hydrogen sulfide poisoning should be suspected whenever a person is found unconscious in an enclosed space, especially if the odor of rotten eggs is noted. The primary target organs of hydrogen sulfide poisoning are those of the central nervous system and respiratory system.

A distinct dose response to hydrogen sulfide is identified. The odor threshold is between 0.02–0.13 ppm, and it has a strong, intense odor at 20–30 ppm. Mild mucous membrane irritation occurs at 50–100 ppm, and olfactory fatigue occurs at 100–150 ppm. Prolonged exposure can occur when the extinction of odor recognition is misinterpreted as dissipation of the gas. Strong irritation of the upper respiratory tract and eyes, as well as acute lung injury, occurs at 200–300 ppm. At greater than 500 ppm, H_2S produces systemic effects. Rapid unconsciousness and cardiopulmonary arrest occur at concentrations greater than 700 ppm.

Neurologic manifestations are common and may be severe. Patients typically lose consciousness at the time of exposure from loss of central respiratory drive. If the patient is removed from the exposure rapidly, recovery may be prompt and complete. Neurologic effects can result from hypoxia secondary to respiratory compromise. Delayed neuropsychiatric sequelae may occur after acute exposures and consist of memory failure (amnestic syndrome), lack of insight, disorientation, delirium, and dementia, transient hearing impairment, vision loss, and anosmia. Motor symptoms are likely caused by injury of the basal ganglia and result in ataxia, position/intention tremor, and muscle rigidity. Common neuropathologic findings observed on CT scan and at autopsy are subcortical white matter demyelination and globus pallidus degeneration.

Diagnostic Testing

Because there is no rapid method of detection that is of clinical diagnostic use, management decisions must be made based on history, clinical presentation, and diagnostic tests that infer the presence of hydrogen sulfide. At the bedside, the smell of rotten eggs on clothing or emanating from the blood, exhaled air, or gastric secretions suggests hydrogen sulfide exposure. In addition, darkening of silver jewelry is a clue to exposure.

In acute poisoning, readily available diagnostic tests that are biomarkers of hydrogen sulfide poisoning may be useful but nonspecific. An arterial blood gas analysis demonstrates metabolic acidosis with an associated elevated se-

TABLE 121–1. Hydrogen Sulfide Poisoning: Emergency Management

Supportive care
Prehospital
Attempt rescue only if using SCBA
Move victim to fresh air
Administer 100% oxygen
During extrication, consider traumatic injuries from falls
Apply ACLS protocols as indicated
Emergency department
Maximize ventilation and oxygenation
Consider PEEP for ALI
Treat acidosis based on arterial pH and serum bicarbonate analysis
Administer crystalloid and vasopressors for hypotension
Antidote
Give sodium nitrite (3% $NaNO_2$) IV over 2–4 minutes
Adult dose: 10 mL (300 mg)
Pediatric dose: see Antidotes in Brief: Sodium and Amyl Nitrite
Caution:
Monitor blood pressure frequently
Obtain methemoglobin concentration 30 minutes after dose
Consider HBO if immediately available

rum lactate concentration, and a normal oxygen saturation, unless acute lung injury is present. Hydrogen sulfide, like cyanide, decreases oxygen consumption and is reflected as an elevated mixed venous oxygen measurement.

Clinical laboratory tests may be useful for confirming exposure but are not readily available for clinical decision making following an acute exposure. Whole-blood sulfide concentrations greater than 0.05 mg/L are considered abnormal.

Management

Table 121–1 summarizes treatment for hydrogen sulfide poisoning. Treatment requires optimal supportive care. Treatments and antidotes beyond supportive care are not of proven clinical benefit. Because hydrogen sulfide toxicity is severe, and case reports suggest the occurrence of delayed sequelae, the potential benefits of nitrite therapy and hyperbaric oxygen should be considered for seriously ill patients exposed to hydrogen sulfide.

Sodium and Amyl Nitrite

HISTORY

The first reference to the antidotal effect of amyl nitrite on cyanide poisoning occurred in 1888. By 1895, the beneficial effects of sodium thiosulfate were well known. By 1933 sodium nitrite was used in patient care. The first case series of combined antidotal therapy with nitrites and thiosulfate occurred in 1949.

MECHANISM OF ACTION

Cyanide quickly and reversibly binds to the ferric iron in cytochrome oxidase, inhibiting effective energy production throughout the body. The ferric iron in methemoglobin preferentially combines with cyanide, producing cyanomethemoglobin. This drives the reaction toward cyanomethemoglobin and liberates cyanide from cytochrome oxidase. Although other mechanisms may be responsible for their antidotal effects, nitrites oxidize the iron in hemoglobin to produce methemoglobin. Although other methemoglobin inducers are effective cyanide antidotes, when methylene blue is administered to prevent methemoglobin formation, nitrite is still effective. Vasodilation might be part of the mechanism of action as nitrites can be converted to nitric oxide, a potent vasodilator. This conversion to nitric oxide appears to only occur in tissues or blood with the lowest oxygen concentrations.

The administration of sodium nitrite should always be followed by sodium thiosulfate. Sodium thiosulfate donates a sulfur, which helps rhodanese (cyanide sulfur transferase) to detoxify circulating cyanide by producing thiocyanate. Thiocyanate is a much less toxic substance than cyanide and is renally eliminated.

PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetics of sodium nitrite have not been established. Most studies have been directed at measuring methemoglobin concentrations as opposed to nitrite concentrations.

CLINICAL USE

As early as 1952, there were reports of 16 patients who had either ingested a cyanide salt or who had been exposed to hydrocyanic acid as a fumigant and survived with the administration of nitrites and sodium thiosulfate. Even patients who were unconscious or apneic have survived with timely cardiopulmonary resuscitation (CPR) and antidotal therapy. Controlled human trials have not occurred.

ADVERSE EFFECTS

Sodium nitrite works by inducing methemoglobinemia. Because too much methemoglobinemia is also potentially lethal, administration of nitrites must be carefully calculated and administered, especially in cases where other coexisting conditions might compromise hemoglobin oxygen saturation, such as carboxyhemoglobin, sulfhemoglobin, and anemia. Children are particu-

larly at risk for medication errors because of dosage miscalculations. Intravenous sodium nitrite 300 mg in healthy adults can produce peak methemoglobin concentrations of 10–18%. Inhalation of crushed amyl nitrite ampoules in human volunteers produces insignificant amounts of methemoglobin, but does cause headache, fatigue, dizziness, and hypotension.

Nitrites are potent vasodilators and therefore transient hypotension may occur. Other adverse effects include headache, nausea, and vomiting.

Administration and Dosing

Cyanide

Adults

Amyl nitrite can be used prior to IV administration of sodium nitrite, but only as a temporizing measure until the IV sodium nitrite can be administered. Break 1 amyl nitrite ampule and hold it in front of the patient's mouth for 15 seconds on and 15 seconds off. Inhalation of amyl nitrite should be discontinued prior to sodium nitrite administration. Healthcare providers should avoid breathing in the amyl nitrite. Sodium nitrite 300 mg (10 mL of a 3% solution) should be injected intravenously at the rate of 2.5–5 mL/min. The dose can be repeated at one-half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis. Immediately following the sodium nitrite infusion, 12.5 g (50 mL of a 25% solution) of sodium thiosulfate should be infused IV. The same needle and vein may be used. The dose can be repeated at one-half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.

Children

Amyl nitrite can be used as a temporizing measure as described above. Once an intravenous line is established, 6–8 mL/m^2 of a 3% solution (approximately 0.2 mL/kg or 6 mg/kg) of sodium nitrite should be infused slowly. The total should not exceed 10 mL or 300 mg. Repeat dosing is as described for adults. Immediately following the sodium nitrite infusion, 7 g/m^2 or 0.5 g/kg (2 mL/kg) of a 25% solution of sodium thiosulfate, not to exceed the adult dose of 12.5 g (50 mL of a 25% solution) of sodium thiosulfate, should be infused intravenously. Repeat dosing is as described for adults.

For either adults or children, in situations where the additional formation of methemoglobin would be harmful, such as smoke inhalation from a fire where other toxic gases may coexist, the nitrite can be withheld and just the sodium thiosulfate administered, or if hydroxocobalamin is available, sodium thiosulfate can then be administered following the hydroxocobalamin.

AVAILABILITY

Sodium nitrite is available in ampules containing 300 mg in 10 mL (3% concentration) of water for injection (USP). It contains no additives or preservatives. It is also available in a kit containing 2 ampules of sodium nitrite with 12 ampules of amyl nitrite inhalants (0.3 mL) and 2 vials of sodium thiosulfate 12.5 g in 50 mL of water for injection (USP), with boric acid or sodium hydroxide added to adjust the pH.

Sodium Thiosulfate

HISTORY

Animal experiments in 1933 demonstrated that intravenous sodium thiosulfate was able to protect against three minimum lethal doses of sodium cyanide. Even more remarkable was the synergistic effects of combining sodium thiosulfate with either inhaled amyl nitrite or intravenous sodium nitrite, which protected the dogs against 10–18 minimum lethal doses of cyanide.

MECHANISM OF ACTION

The sulfur provided by sodium thiosulfate binds to cyanide with the help of rhodanese (cyanide sulfur transferase), mercaptopyruvate sulfurtransferase, and serum albumin, producing thiocyanate. Thiocyanate, a minimally toxic substance, is then renally eliminated. Experimental addition of rhodanese increases the efficacy of sodium thiosulfate, but is impractical in the clinical setting. An additional theory proposes that both mercaptopyruvate sulfurtransferase and rhodanese are involved with the formation of sulfane sulfur in the liver from sodium thiosulfate and that serum albumin then carries the sulfur from the liver to other organs. When cyanide is present, albumin delivers this sulfur to cyanide forming thiocyanate.

PHARMACOKINETICS AND PHARMACODYNAMICS

Animal Studies

Sodium thiosulfate rapidly distributes into the extracellular space and then slowly into the cell, with perhaps a carrier facilitating entry into the mitochondria. When administered prior to cyanide, thiosulfate was able to convert more than 50% of the cyanide to thiocyanate within 3 minutes and increased the endogenous conversion rate more than 30 times. Thiosulfate is filtered in the kidney and then secreted, and at low plasma concentrations, it is largely reabsorbed. At high plasma concentrations, filtration and secretion predominate.

Human Volunteers

Oral sodium thiosulfate is poorly absorbed and acts as a laxative. After injection of 150 mg/kg, the volume of distribution (Vd) was 0.15 L/kg, the distribution half-life was 23 minutes, and the elimination half-life was 3 hours. Approximately 50% of the drug was eliminated in the urine in 18 hours, with most occurring within 3 hours. Normally the kidney actively reabsorbs thiosulfate, but with exogenous administration this study found that thiosulfate clearance equaled creatinine clearance.

CLINICAL USE

Cyanide

As early as 1952, there were reports of 16 patients who had either ingested a cyanide salt or been exposed to hydrocyanic acid as a fumigant and survived with the administration of nitrites and sodium thiosulfate. Even patients who were unconscious or apneic survived with timely cardiopulmonary resuscita-

tion (CPR) and antidotal therapy. There are only a few case reports where cyanide was ingested and sodium thiosulfate was used alone. Those cases all had favorable outcomes. We advocate the use of amyl or sodium nitrite, or hydroxocobalamin, if available, prior to sodium thiosulfate, unless the methemoglobin produced by the administration of sodium nitrite is potentially dangerous as might occur following smoke inhalation, in which case nitrites should be withheld (see Antidotes in Brief: Sodium and Amyl Nitrite).

Nitroprusside

Following high doses of nitroprusside, cyanide concentrations in the blood begin to rise. Coadministration of sodium thiosulfate with sodium nitroprusside in a 5:1 molar ratio (as nitroprusside contains five cyanide ions), prevents the rise in cyanide.

ADVERSE EFFECTS

The toxicity of sodium thiosulfate is quite low. The LD_{50} (median lethal dose for 50% of test subjects) listed in animals is around 3–4 g/kg, with death attributed to metabolic acidosis, elevated sodium concentration, decreased blood pressure, and decreased PO_2. Adverse effects associated with therapeutic dosing include hypotension, nausea, and vomiting. The osmotic and diuretic effects are presumably both from the formation of thiocyanate and the intrinsic osmotic properties of the drug.

ADMINISTRATION AND DOSING

Cyanide

Adults

In most circumstances, either amyl nitrite or sodium nitrite, or both, or hydroxocobalamin should be given before sodium thiosulfate (see Antidotes in Brief: Sodium and Amyl Nitrite). The adult dose of sodium thiosulfate is 12.5 g (50 mL of a 25% solution) administered intravenously either as a bolus injection or infused over 10–30 minutes, depending on the severity of the situation. One-half the initial dose can be repeated if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.

Hydroxocobalamin is preferred when elevated methemoglobin levels pose a risk. When hydroxocobalamin is combined with sodium thiosulfate, its synergistic effects are ideal. When the formation of methemoglobin would not be detrimental, a combination of hydroxocobalamin, sodium nitrite, and sodium thiosulfate would be advantageous.

Children

In most circumstances, either amyl nitrite or sodium nitrite, or both, should be given before sodium thiosulfate (see Antidotes in Brief: Sodium and Amyl Nitrite). The dose of sodium thiosulfate in children is 7 g/m^2 up to the adult dose, or 0.5 g/kg (2 mL/kg of a 25% solution) up to the adult dose of 12.5 g (50 mL of a 25% solution). One-half the initial dose can be repeated if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.

In both adults and children, when the additional formation of methemoglobin would be harmful (such as smoke inhalation), the nitrite can be withheld and just the sodium thiosulfate or hydroxocobalamin administered.

Nitroprusside

Each mole of nitroprusside contains five cyanide ions. Prolonged infusion or doses in excess of the body's detoxifying capability may lead to thiocyanate or cyanide toxicity. A prophylactic dose of 0.5 g of sodium thiosulfate added to each 50 mg of nitroprusside is recommended. Although this dose of sodium thiosulfate is usually sufficient to prevent cyanide toxicity from the nitroprusside, thiocyanate may accumulate, especially in patients with renal insufficiency.

Nitroprusside-induced cyanide toxicity should be treated like cyanide from any other cause; stop the nitroprusside and administer sodium nitrite or hydroxocobalamin, followed by sodium thiosulfate.

AVAILABILITY

Sodium thiosulfate is available in 50 mL vials containing 12.5 g in water for injection, with boric acid or sodium hydroxide added to adjust the pH. It is also available in a kit containing 2 ampules of sodium nitrite (300 mg in 10 mL water for injection) with 12 ampules of amyl nitrite inhalants (0.3 mL) and 2 vials of sodium thiosulfate 12.5 g in 50 mL of water for injection.

Hydroxocobalamin

HISTORY

As early as 1894, the antidotal actions of cobalt as a chelator of cyanide were recognized. The cobalt-containing compound hydroxocobalamin was first used as an antidote to cyanide in mice. Subsequently, hydroxocobalamin was successful in protecting against several minimum lethal doses of cyanide as long as an equimolar ratio of hydroxocobalamin to cyanide was used.

CHEMISTRY

Hydroxocobalamin, is a vitamin B_{12} precursor often referred to as vitamin B_{12a}. The only difference between cyanocobalamin (vitamin B_{12}) and hydroxocobalamin is the replacement of the CN group with an OH group. In vitro studies demonstrated that cyanide displaces the OH group in hydroxocobalamin to form cyanocobalamin.

MECHANISM OF ACTION

The cobalt in hydroxocobalamin combines with cyanide to form the relatively nontoxic cyanocobalamin. One mole of hydroxocobalamin binds 1 mole of CN. Given the molecular weights of each, it requires 52 g of hydroxocobalamin to bind 1 g of cyanide. Use of hydroxocobalamin with sodium thiosulfate is synergistic, and comparable to the sequential use of sodium nitrite with sodium thiosulfate.

PHARMACOKINETICS AND PHARMACODYNAMICS

In healthy volunteers, the half-life of hydroxocobalamin ranges from 1.27–4 hours depending on experimental conditions. Following an intravenous dose of 5 g, peak hydroxocobalamin concentration averages 813 μg/mL (604 μmol/L) and the volume of distribution (Vd) averages 0.38 L/kg. A mean 62% of the dose is recovered in the urine in 24 hours.

The kinetics in adult victims of smoke inhalation are dramatically different. Following an intravenous administration of 5 g over 30 minutes, the elimination half-life was 26.2 hours and the Vd was 0.45 L/kg. Renal clearance of hydroxocobalamin was 37%.

Cyanocobalamin concentrations were analyzed in patients with suspected cyanide poisoning who were given 5 g of hydroxocobalamin intravenously. In patients with cyanide concentrations less than 40 μmol/L (1 μg/mL), a linear relationship existed between the blood cyanide concentration and the formation of cyanocobalamin. In patients with blood cyanide concentrations greater than 40 μmol/L, the formation of cyanocobalamin plateaued, implying that all of the hydroxocobalamin was consumed.

CLINICAL USE

There are many case reports in France that document the efficacy of hydroxocobalamin combined with sodium thiosulfate for the treatment of cyanide toxicity. In one study, 69 patients with smoke inhalation were administered a

mean dose of 8 g of hydroxocobalamin. Two-thirds of the patients with documented cyanide concentrations typically considered fatal, survived.

Hydroxocobalamin was also able to prevent the rise in cyanide concentration following nitroprusside infusion when compared to patients who did not receive hydroxocobalamin. Most animal studies demonstrate a synergistic effect of hydroxocobalamin and thiosulfate.

ADVERSE EFFECTS

Hydroxocobalamin has a very large therapeutic index and appears to be well tolerated. Large doses have been administered to animals with no adverse effects. Red discoloration of mucous membranes, plasma, and urine may occur and may last anywhere from 12 hours to days after therapy. Rarely, allergic reactions are reported. Prior chronic exposure to hydroxocobalamin or cyanocobalamin for treatment of vitamin B_{12} deficiency is associated with the development of anaphylaxis. An in vitro study found statistically significant alterations in serum concentrations of aspartate aminotransferase (AST), total bilirubin, creatinine, magnesium, and iron after hydroxocobalamin administration. Colorimetric assays are most likely to be adversely affected as hydroxocobalamin is an intensely red color, as is cyanocobalamin, the end product of binding hydroxocobalamin to cyanide.

ADMINISTRATION AND DOSING

Cyanide

A dose of 70 mg/kg IV (not to exceed 5 g initially) is given over 30 minutes. This dose may be administered as an intravenous push in cases of cyanide induced cardiac arrest, and can be repeated (not to exceed a total dose of 15 g) as clinically necessary. The second and subsequent doses should be infused intravenously over a longer period (6–8 hours), except in refractory cardiac arrest or collapse.

Sodium thiosulfate is synergistic with hydroxocobalamin and should also be administered separately and consecutively following the administration of hydroxocobalamin (see Antidotes in Brief: Sodium Thiosulfate). When the formation of methemoglobin would not be detrimental, a combination of hydroxocobalamin, sodium nitrite, and sodium thiosulfate should be studied to determine if triple therapy is advantageous.

The hydroxocobalamin solution should not be administered through the same infusion and at the same time as a thiosulfate solution, as sodium thiosulfate binds to hydroxocobalamin, rendering it inactive.

AVAILABILITY

Hydroxocobalamin was approved by the FDA in late 2006 for the treatment of cyanide poisoning. It is marketed under the name Cyanokit and includes two vials, each of which contains 2.5 g of hydroxycobalamin as a lyophylized powder, which should be reconstituted in 100 mL of 0.9% sodium chloride and infused intravenously over 15 minutes to 2 hours depending on the patient's condition.

122 Methemoglobin Inducers

Methemoglobin occurs when the iron atom in hemoglobin loses 1 electron to an oxidant, and the ferrous (Fe^{2+}) state of iron is transformed into the ferric (Fe^{3+}) state. Although methemoglobin is always present at low concentrations in the body, methemoglobinemia is defined herein as an abnormal elevation of methemoglobin.

HISTORY AND EPIDEMIOLOGY

Methemoglobin was first described in 1864. In 1948, an enzyme defect was reported in twin brothers that caused cyanosis, in the absence of cardiopulmonary disease, and was responsive to ascorbic acid therapy. Methemoglobinemia can be hereditary or acquired. The hereditary types are rare, with only several hundred cases reported. A recent review identified benzocaine spray and dapsone as the major pharmaceutical causes of methemoglobinemia.

HEMOGLOBIN PHYSIOLOGY AND METHEMOGLOBIN

Hemoglobin consists of 4 polypeptide chains noncovalently attracted to each other. Each of these subunits carries 1 heme molecule deep within the structure. The polypeptide chain protects the iron moiety of the heme molecule from inappropriate oxidation. The iron is held in position by 6 coordination bonds. Four of these bonds are between iron and the nitrogen atoms of the protoporphyrin ring, with the fifth and sixth bond sites lying above and below the protoporphyrin plane. The fifth site is occupied by histidine of the polypeptide chain. Changes in the amino acid sequence of the polypeptide chain, as occur in hemoglobin M, influence this protective "pocket," allowing easier iron oxidation. The sixth coordination is the site of oxygen transport, and is involved with formation of methemoglobin or carboxyhemoglobin. Hemoglobin will transport an oxygen molecule only when its iron atom is in the reduced or ferrous state (Fe^{2+}).

METHEMOGLOBIN PHYSIOLOGY AND KINETICS

Because of spontaneous oxidation of hemoglobin, erythrocytes have multiple mechanisms to maintain the normal concentration of methemoglobin at less than 1%. All of these systems donate an electron to the oxidized iron atom. Quantitatively the most important reductive system requires nicotinamide adenine dinucleotide (NADH). NADH serves as an electron donor, and along with the enzyme NADH methemoglobin reductase (cytochrome b_5 reductase), reduces the oxidized ferric (Fe^{3+}) iron to the ferrous (Fe^{2+}) iron state. There are numerous cases of hereditary deficiencies of the enzyme NADH methemoglobin reductase. Additionally, because this enzyme system lacks full activity until about 4 months of age, infants are more susceptible than adults to oxidizing stresses. Oxidized iron can be reduced nonenzymatically using ascorbic acid and reduced glutathione as electron donors, but this is slow and quantitatively less important.

Within the red cell another enzyme uses nicotinamide-adenine dinucleotide phosphate (NADPH) to reduce methemoglobin (Fig. 122–1). Although

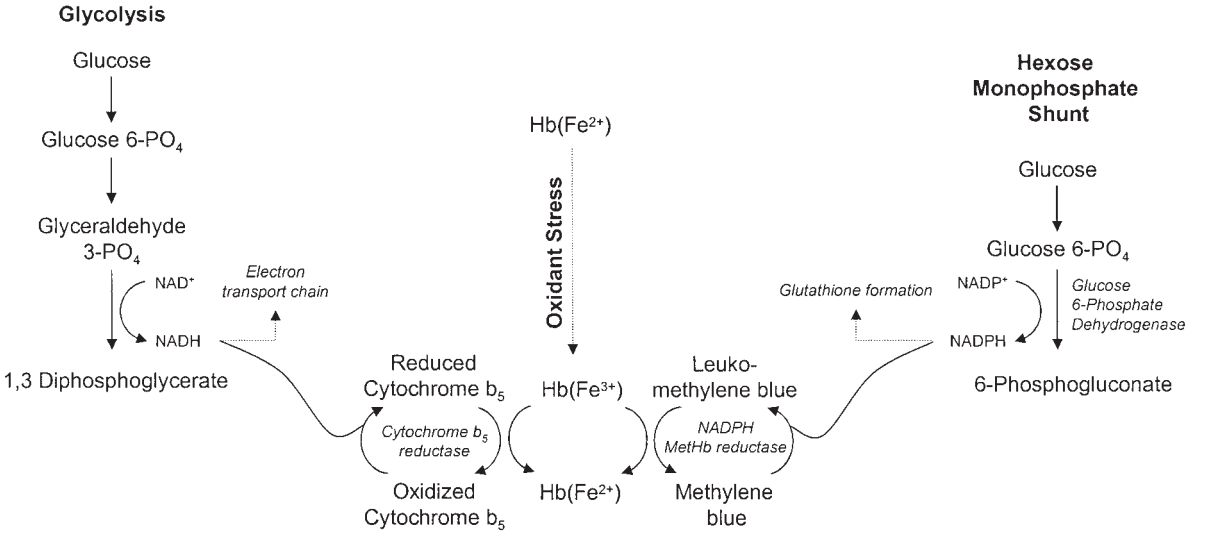

FIG. 122–1. Role of glycolysis in the Embden-Meyerhof pathway and the role of methylene blue in the reduction of methemoglobin.

this pathway has a relatively minor role in methemoglobin reduction under normal circumstances. When NADPH methemoglobin reductase system is provided with an exogenous electron carrier such as methylene blue, this system is accelerated and becomes the primary method of detoxification (see Antidotes in Brief: Methylene Blue).

Table 122–1 lists common etiologies for methemoglobinemia. The half-life of methemoglobin acutely formed as a result of exposure to oxidants is 1–3 hours. If there is continuous exposure to the oxidant, then the half-life of methemoglobin will appear prolonged. Certain compounds, such as dapsone, characteristically produce prolonged methemoglobinemia.

TABLE 122–1. Common Etiologies of Methemoglobinemia

Hereditary

Hemoglobin M
Cytochrome b_5 reductase deficiency (homozygote and heterozygote)

Acquired

A. Medications
Amyl and sodium nitrite
Benzocaine
Dapsone
Lidocaine
Nitric oxide
Nitroglycerin
Nitroprusside
Phenacetin
Phenazopyridine
Prilocaine (local anesthetic)
Quinones (chloroquine, primaquine)
Sulfonamides (sulfanilamide, sulfathiazide, sulfapyridine, sulfamethoxazole)

B. Other xenobiotics
Aniline dye derivatives (shoe dyes, marking inks)
Butyl nitrite
Chlorobenzene
Fires (heat-induced denaturation)
Food adulterated with nitrites
Food high in nitrates
Isobutyl nitrite
Naphthalene
Nitrates
Nitrites
Nitrophenol
Nitrous gases (seen in arc welders)
Silver nitrate
Trinitrotoluene
Well water (nitrates)

Pediatric

Reduced NADH methemoglobin reductase activity in infants (<4 months). Associated with low birth weight, prematurity, dehydration, acidosis, diarrhea, and hyperchloremia.

CLINICAL MANIFESTATIONS

The clinical manifestations of methemoglobinemia are related to impaired oxygen carrying and delivery to the tissue. As methemoglobin is unable to bind oxygen, a functional anemia is created. In addition, methemoglobin increases the affinity of the unaltered hemoglobin for oxygen (it shifts the oxygen hemoglobin dissociation curve to the left), which further impairs oxygen delivery (Chap. 22). Because the symptomatology associated with methemoglobinemia is related to impaired oxygen delivery to the tissue, concurrent diseases, such as anemia, congestive heart failure, chronic obstructive pulmonary disease, and pneumonia, may greatly increase the clinical effects of methemoglobinemia (Fig. 122–2).

Cyanosis is a consistent physical finding and typically occurs when just 1.5 g/dL of methemoglobin is present, which represents approximately a 10% methemoglobinemia. At 20–50% methemoglobin concentrations, dizziness, fatigue, headache, and exertional dyspnea may develop. At approximately 50% methemoglobin, lethargy and stupor usually appear; and the lethal concentration is probably greater than 70% (Table 122–2).

DIAGNOSTIC TESTING

Arterial blood gas sampling may reveal blood with a characteristic chocolate brown color. The arterial PO_2 should be normal reflecting the adequacy of pulmonary function to deliver dissolved oxygen to the blood. However, the arterial PO_2 does not measure the more important physiologic parameter, the hemoglobin oxygen saturation (SaO_2) or oxygen content of the blood. When the partial pressure of oxygen is known, and oxyhemoglobin and deoxyhemoglobin are the only species of hemoglobin, oxygen saturation can be calculated accurately from the arterial blood gas. If, however, other hemoglobins are present, such as methemoglobin, sulfhemoglobin, or carboxyhemoglobin, then the fractional saturation of the hemoglobin must be determined by the cooximeter.

Methemoglobin interferes with standard pulse oximetry in a complicated fashion. The degree of inaccuracy is unique for each brand of instrument, and may be influenced by signal quality, skin temperature, refractive error induced by blood cells, and other issues, such as finger thickness and perfusion. In general, the pulse oximeter oxygen saturation (SpO_2) values drop with increasing methemoglobin concentrations and tend to approach 85%. From our experience and that of others, much lower concentrations of oxygen saturation (SpO_2) than 85% can occur by pulse oximetry when methemoglobin concentrations rise above 30%, but these concentrations are still not representative of true oxygen saturation (Table 122–3). Newer pulse oximeters have the ability to correctly identify methemoglobin.

METHEMOGLOBINEMIA AND HEMOLYSIS

Hemolysis and methemoglobinemia are both caused by oxidant stress, and hemolysis can occur following episodes of methemoglobinemia. The enzyme defect responsible for oxidant-induced hemolysis is a deficiency in glucose-6-phosphate dehydrogenase. Oxidants damage the erythrocyte at different locations in the two disease entities. Hemolysis occurs when oxidants damage the hemoglobin chain acting directly, causing denaturation and precipitation of the protein. These precipitates form Heinz bodies within the erythrocyte that are removed by the reticuloendothelial system, fragmenting cells to produce hemolysis.

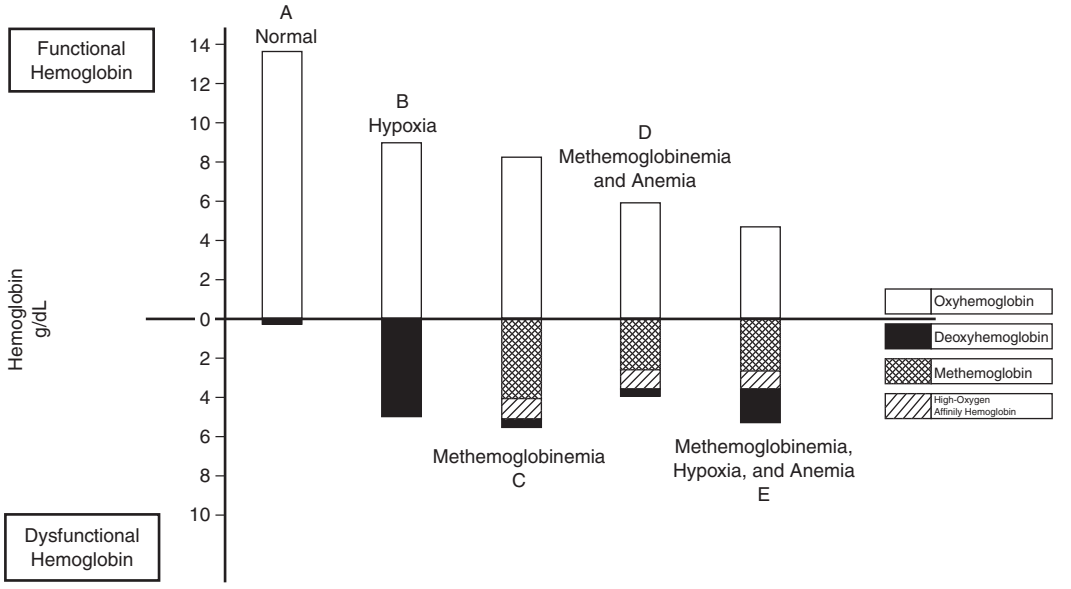

FIG. 122–2. Clinical manifestations of methemoglobinemia depend on the concentration of methemoglobinemia and on host factors such as preexisting disease, anemia and hypoxemia. Five examples of arterial blood gas and cooximeter analyses are presented. **A.** Blood gas from a normal individual with 14 g/dL of hemoglobin. Almost all hemoglobin is saturated with oxygen. **B.** Blood gas from a patient with cardiopulmonary disease producing cyanosis in which only 9 g/dL of hemoglobin is capable of oxygen transport. **C.** Methemoglobin concentration of 28% in an otherwise normal individual will reduce hemoglobin available for oxygen transport to <9 g/dL (approximately 4 g/dL of methemoglobin and 1.3 g/dL of high-oxygen-affinity hemoglobin because of the left shift of the oxyhemoglobin dissociation curve). **D.** Same degree of methemoglobin as in *C* but in a patient with a hemoglobin of 10 g/dL. Only 6 g/dL of hemoglobin would be capable of oxygen transport. **E.** Methemoglobinemia and anemia to the same degree as *D,* but in a hypoxic patient.

TABLE 122–2. Signs and Symptoms Typically Associated with Methemoglobin Concentrations in Healthy Patients with Normal Hemoglobin Concentrations

Methemoglobin Concentration (%)	Signs and Symptoms
1–<3 (Normal)	None
3–15	Possibly none Slate gray cutaneous coloration Pulse oximeter will read low SaO_2
15–19	Cyanosis Chocolate brown blood
20–49	Dyspnea Exercise intolerance Headache Fatigue Dizziness, syncope Weakness
50–69	Tachypnea Metabolic acidosis Dysrhythmias Seizures CNS depression Coma
>70	Grave hypoxic symptoms Death

MANAGEMENT

Figure 122–3 summarizes the approach to patients with methemoglobinemia. For most patients with mild methemoglobinemia, no therapy is necessary other than withdrawal of the offending xenobiotic, as reduction of the methemoglobin will occur by means of intact normal reconversion mechanisms (NADH methemoglobin reductase). Patients should be examined carefully for signs of physiologic stress related to decreased oxygen delivery to the tissue. Obviously, changes in mental status or ischemic chest pain necessitate immediate treatment, but subtle changes in behavior or inattentiveness also may be signs of global hypoxia and should be treated as well. Abnormal vital signs, such as tachycardia and tachypnea, or lactic acidosis thought to be caused by tissue hypoxia or the functional anemia of methemoglobinemia, should also be treated aggressively. A methemoglobin concentration alone is generally not an adequate independent indication of need for therapy.

The treatment of methemoglobinemia is the administration of methylene blue, 1–2 mg/kg body weight infused IV over 5 minutes. This is 0.1–0.2 mL/kg of a 1% solution. Clinical improvement should be noted within 30 minutes. Methylene blue causes a transient decrease in the pulse oximetry reading because of its blue color and excellent absorption at 660 mm (see Antidotes in Brief: Methylene Blue).

Theoretically, exchange transfusion or hyperbaric oxygen may be beneficial when methylene blue is ineffective. Both interventions are time-consuming and costly, but hyperbaric oxygen offers the alternative of allowing the dissolved oxygen time to protect the patient while endogenous methemoglobin reduction occurs. Ascorbic acid is not indicated in the management of acquired methemoglobinemia because the rate at which it reduces methemoglobin is considerably slower than that of the normal intrinsic mechanisms.

TABLE 122–3. Hemoglobin Oxygenation Analysis

Measuring Device	Source	What is Measured?	How Are Data Expressed?	Benefits	Pitfalls	Insight
Blood gas analyzer	Blood	Partial pressure of dissolved oxygen in whole blood	PO_2	Also gives information about pH and PCO_2	Calculates SaO_2 from the partial pressure of oxygen in plasma; inaccurate if forms of Hb other than OxyHb and DeoxyHb are present	An abnormal Hb form may exist if gap exists between ABG and pulse oximeter
Cooximeter	Blood	Directly measures absorptive characteristics of oxyhemoglobin, deoxyhemoglobin, methemoglobin, carboxyhemoglobin at different wavelength bands in whole blood	SaO_2 % MethHb, % CoHb, % OxyHb, % DeoxyHb	Measures hemoglobin species directly	Provides data on hemoglobin only; some newer instruments will measure sulfhemoglobin, HbM, and some other forms of Hb	Most accurate method to determine oxygen content of blood
Standard pulse oximeter[a]	Monitor sensor on patient	Absorptive characteristics of oxyhemoglobin in pulsatile blood assuming the presence of only OxyHb and DeoxyHb in vivo	SpO_2	Moment-to-moment bedside data	Inaccurate data, if interfering substances are present: methemoglobin, sulfhemoglobin, carboxyhemoglobin, methylene blue	Maximum depression 75–85%, regardless of how much methemoglobin is present

[a]Some newer devices can reliably detect carboxyhemoglobin and methemoglobin.

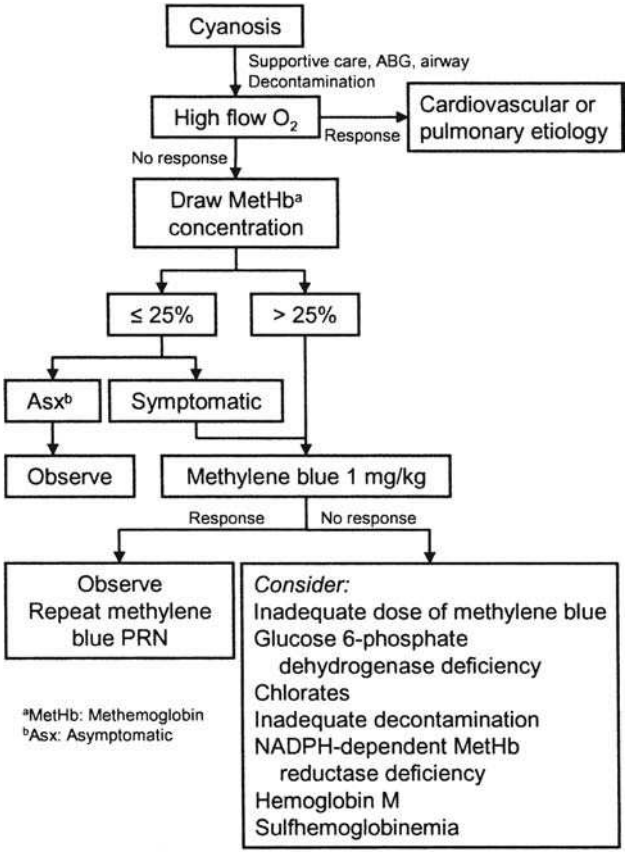

FIG. 122–3. Toxicologic assessment of the cyanotic patient.

SPECIFIC MANAGEMENT FOR DAPSONE-INDUCED METHEMOGLOBINEMIA

The treatment of dapsone induces methemoglobinemia deserves special consideration because of the frequency in which it occurs and its tendency to produce prolonged methemoglobinemia. The *N*-hydroxylation of dapsone to its hydroxylamine metabolite by a cytochrome P450 mediated reaction is in part responsible for methemoglobin formation, both in therapeutic and overdose situations. Both the parent compound and its metabolites are oxidants with long half-lives. Cimetidine is an inhibitor of this metabolic pathway and reduces methemoglobin concentrations during therapeutic dosing. It may be considered for therapy of acute overdose as well. There may also be a role for multiple dose activated charcoal therapy.

SULFHEMOGLOBIN

Sulfhemoglobin is a hemoglobin variant in which a sulfur atom is incorporated into the heme molecule but not attached to iron. Sulfhemoglobin is a

darker pigment than methemoglobin, producing cyanosis when only 0.5 g/dL of blood is affected. Sulfhemoglobin also produces a drop in pulse oximetry readings. Sulfhemoglobin is an extremely stable compound that is eliminated only when the red blood cell is removed naturally from circulation. Although the oxygen carrying capacity of hemoglobin is reduced by sulfhemoglobinemia, unlike methemoglobinemia there is a decreased affinity for oxygen in the remaining "unaltered" hemoglobin. The oxyhemoglobin dissociation curve is shifted to the right, which makes oxygen more available to the tissues. This phenomenon, fortunately, reduces the clinical effect of sulfhemoglobin at the tissue level.

A number of drugs induce sulfhemoglobin in humans, including nitrates, trinitrotoluene, and sulfur compounds. Most of the drugs that produce methemoglobinemia have been reported, in various degrees, to produce sulfhemoglobinemia.

Sulfhemoglobinemia usually requires no therapy other than the withdrawal of the offending xenobiotic. There is no antidote for sulfhemoglobinemia because it is an irreversible chemical bond that occurs within the hemoglobin molecule. Exchange transfusion would lower sulfhemoglobin concentrations, but this approach is usually unnecessary.

Methylene Blue

HISTORY

Methylene blue was initially recommended for use as an intestinal and urinary antiseptic, and subsequently recognized as a weak antimalarial agent. Subsequently, methylene blue was used to treat aniline induced methemoglobinemia.

PHARMACOLOGY

Methylene blue is an oxidizing agent, which in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and NADPH methemoglobin reductase is reduced to leukomethylene blue. Leukomethylene blue then becomes available to reduce methemoglobin to hemoglobin. Reduction of methemoglobin via this NADPH pathway is limited under normal circumstances. However, in the presence of methylene blue, the pathway's role is dramatically increased and becomes the most efficient means of methemoglobin reduction. This property makes methylene blue the treatment of choice for methemoglobinemia.

PHARMACOKINETICS

Methylene blue exhibits complex pharmacokinetics consistent with extensive distribution into deep compartments followed by a slower terminal elimination with a half-life of 5.25 hours. Extensive first-pass distribution limits peak concentrations following oral administration. Total urinary excretion at 24 hours accounts for 28.6% of the dose after IV administration.

ADVERSE EFFECTS

Reports of the apparent paradoxical ability of methylene blue to induce methemoglobinemia suggest an equilibrium between the ability of methylene blue to oxidize hemoglobin directly to methemoglobin and the ability of methylene blue (through the NADPH and NADPH methemoglobin reductase pathway and leukomethylene blue production) to reduce methemoglobin to hemoglobin. The equilibrium seems to favor the reducing properties of methylene blue unless excessively large doses of methylene blue are administered or the NADPH methemoglobin reductase system is abnormal. Methemoglobin does not occur at doses of 1–2 mg/kg. It is generally recommended to avoid doses in excess of 7 mg/kg. Consequential adverse effects, with excessive doses, include shortness of breath, tachypnea, chest discomfort, burning sensation of the mouth and stomach, initial bluish-tinged skin and mucous membranes, paresthesias, restlessness, apprehension, tremors, nausea and vomiting, dysuria, and excitation. Urine and vomitus have a blue color. Consistent with its oxidant effects, high doses of methylene blue can also induce an acute hemolytic anemia independent of the presence of methemoglobinemia.

Since methylene blue is a pigment, it will alter pulse oximeter readings. Large doses may interfere with the ability to detect a clinical decrease in cyanosis; consequently, repeat cooximeter measurements and arterial blood gas analysis should be used in conjunction with clinical findings.

USE IN PATIENTS WITH GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Methylene blue is suggested to be ineffective in reversing methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency because G6PD is essential for the generation of NADPH (Chap. 24). Without NADPH, methylene blue cannot act in the reduction of methemoglobin. However, G6PD deficiency is an X-linked hereditary deficiency with more than 400 variants. Currently, it appears that most individuals have adequate G6PD and express deficiency states in relative terms. This variable expression of their deficiency allows an effective response to methylene blue in most patients. Theoretically, normal cells might convert methylene blue to leukomethylene blue, and the leukomethylene blue might diffuse into G6PD deficient cells and effectively reduce methemoglobin to hemoglobin.

Before it is assumed that G6PD deficiency is responsible for continued methemoglobin concentrations in spite of the administration of methylene blue, continued xenobiotic absorption and/or continued methemoglobin production must always be excluded. However, when therapeutic doses of methylene blue fail to have an impact on the methemoglobin concentration, the possibility of G6PD deficiency should be considered. Further doses of methylene blue should not be administered in these cases because of the risk of methylene blue induced hemolysis. In these cases, exchange transfusion and hyperbaric oxygen are potential alternatives (Chap. 122).

DOSING

Methylene blue is indicated in patients with symptomatic methemoglobinemia. This usually occurs at methemoglobin concentrations greater than 20%, but may occur at lower concentrations in anemic patients or those with cardiovascular, pulmonary, or central nervous system compromise.

In most cases, doses of 1–2 mg/kg IV given over 5 minutes, followed immediately by a 15–30-mL fluid flush to minimize local pain is both effective and relatively safe. In neonates, doses of 0.3–1 mg/kg are often effective. The onset of action is quite rapid, and maximal effects usually occur within 30 minutes. Repetitive dosing of methylene blue may be required in conjunction with efforts to decontaminate the GI tract when there is continued absorption or slow elimination of the xenobiotic producing the methemoglobinemia, such as with dapsone.

Intraosseous administration into the anterior tibia of a 6-week-old infant of 0.3 mL of a 1% solution (1 mg/kg) of methylene blue over 3–5 minutes was well tolerated.

AVAILABILITY

Methylene blue is available in 10-mL 1% ampules containing 10 mg/mL.

123 Smoke Inhalation

HISTORY AND EPIDEMIOLOGY

Smoke is a complex mixture of heated air, suspended solid and liquid particles, gases, fumes, aerosols, and vapors. Smoke inhalation is the leading cause of death as a consequence of fires. In the United States, every 20 seconds a fire department responds to a fire. In 2003, the National Fire Protection Agency reported 1,584,500 fire incidents in the United States with 3925 fire deaths and 18,125 fire injuries. An estimated 50–80% of these fire deaths are a result of smoke inhalation injuries rather than burns or trauma. More than 30% of patients hospitalized in burn units develop concomitant pulmonary complications, and of these, 75% die.

PATHOPHYSIOLOGY

Many common household products produce toxins when burned (Table 123–1). These toxic combustion products are classified into 3 categories: simple asphyxiants, irritant toxins, and chemical asphyxiants (Table 123–2). Simple asphyxiants exert a space-occupying effect, simply displacing oxygen. In addition, combustion uses oxygen, potentially resulting in an oxygen-deprived environment (Chap. 119). Irritant toxins are chemically reactive compounds that exert a local effect on the respiratory tract (Chap. 119). The chemical asphyxiants interfere with oxygen transport and use at sites remote from the respiratory tract (Chaps. 120, 121, and 122). In addition, combustion of organic material produces finely divided carbonaceous particulate matter (soot) suspended in hot air and gases. Inhalation of soot particles and aerosols enhance the exposure to irritant toxins in a fire environment, as many toxins are adsorbed to their surfaces. Soot adheres to the mucosa of the airways, allowing adsorbed irritant chemicals to react with the mucosal surface moisture.

Following more than a trivial exposure to water-soluble irritants, the intense inflammatory response increases microvascular permeability and allows movement of fluid from the intravascular space into the tissues of the upper airway. The loosely attached underlying tissue of the supraglottic larynx can become markedly edematous causing upper airway obstruction within minutes to hours. Low-water-solubility irritants react with the upper-respiratory mucosa very slowly and reach the distal lung parenchyma, where they react slowly. Tracheobronchial injuries are caused by inhaled particulates and by toxic gases causing increased airway resistance from intraluminal debris, airway mucosal edema, inspissated secretions, and bronchospasm. In victims of smoke inhalation, casts block major airways, increasing airway resistance and mechanically preventing passage of oxygen to the alveoli. Increased tracheobronchial vascular permeability leads to interstitial edema of the airways and increased airway resistance. Bronchoconstriction and subsequent wheezing are caused by a response to mediators of inflammation—a reflex response to toxic mucosal injury.

CLINICAL MANIFESTATIONS

The primary clinical problem in the smoke inhalation victim is respiratory compromise. The patient may have voice changes and the patient's speech may progressively worsen as the airway becomes increasingly edematous.

TABLE 123–1. Common Materials and Their Combustion Products

Products	Combustion Products
Wool	Carbon monoxide, hydrogen chloride, phosgene, chlorine, cyanide
Silk	Sulfur dioxide, hydrogen sulfide, ammonia, cyanide
Nylon	Ammonia, cyanide
Wood, cotton, paper	Carbon monoxide, acrolein, acetaldehyde, formaldehyde, acetic acid, formic acid, methane
Petroleum products	Carbon monoxide, acrolein, acetic acid, formic acid
Polystyrene	Styrene
Acrylic	Acrolein, hydrogen chloride, carbon monoxide
Plastics	Cyanide, hydrogen chloride, aldehydes, ammonia, nitrogen oxides, phosgene, chlorine
Polyvinyl chloride	Carbon monoxide, hydrogen chloride, phosgene, chlorine
Polyurethane	Cyanide, isocyanates
Melamine resins	Ammonia, cyanide
Rubber	Hydrogen sulfide, sulfur dioxide
Sulfur-containing material	Sulfur dioxide
Nitrogen-containing material	Cyanide, isocyanates, oxides of nitrogen
Fluorinated resins	Hydrogen fluoride
Fire-retardant materials	Hydrogen chloride, hydrogen bromide

Stridor and respiratory arrest may develop. The patient may have difficulty managing airway secretions, with copious quantities of soot-containing sputum being expectorated. Visualization of the vocal cords by direct laryngoscopy may be difficult because of soot accumulation, secretions, or edema.

Auscultation of the chest may demonstrate rhonchi, rales, and wheezing suggestive of acute lung injury (ALI). The most severe manifestation of ALI is the acute respiratory distress syndrome (ARDS) and is defined based on the patient's ability to oxygenate (Chap. 22). Bronchospasm may occur, particularly in a patient with underlying reactive airway disease. Tachycardia and tachypnea may be pronounced and hypotension may occur with faint or no

TABLE 123–2. Toxic Combustion Products

Simple Asphyxiants	**Irritants**
Carbon dioxide	High water solubility (upper airway injury)
	Acrolein
Chemical Asphyxiants	Sulfur dioxide
Carbon monoxide	Ammonia
Hydrogen cyanide	Hydrogen chloride
Hydrogen sulfide	Intermediate water solubility
Oxides of nitrogen (methemoglobinemia)	(upper and lower respiratory tract injury)
	Chlorine
	Isocyanates
	Low water solubility
	(pulmonary parenchymal injury)
	Oxides of nitrogen
	Phosgene

peripheral pulses noted. The smoke inhalation victim may develop an altered mental status, including agitation, confusion, or coma. Conjunctival injection, corneal ulcerations, marked lacrimation, and blepharospasm may be noted on ophthalmologic examination.

DIAGNOSTIC TESTING

Because smoke inhalation injury causes pulmonary and airway damage, diagnostic studies should focus on assessing oxygenation and ventilation. Consequently, arterial blood gas (ABG) analysis, carboxyhemoglobin concentration, methemoglobin concentration, and chest radiography are the most important tests to obtain. Transcutaneous measurement of oxygen saturation by pulse oximetry is unreliable in the patient with smoke inhalation because it overestimates oxygen saturation in the presence of carboxyhemoglobin.

The most frequent abnormal findings on initial chest radiograph are diffuse alveolar and interstitial changes found in 34% of patients, followed by focal abnormalities in 12%. In one series, there were no significant differences in the duration of either ventilation or stay in the intensive care unit between smoke inhalation victims who exhibited abnormal findings on the first chest radiographic examination and those without any abnormalities. Subtle findings within 24 hours of exposure include perivascular haziness, peribronchial cuffing, bronchial wall thickening, and subglottic edema. Serial chest radiographs following a baseline study are helpful, as widespread airways disease usually occurs more than 24 hours after injury.

Nuclear imaging and pulmonary function testing, although not readily available for initial evaluation, can detect pulmonary injury after smoke inhalation. Xenon ventilation studies can detect small airway and alveolar injury before radiographic changes occur. Abnormal flow volume curves can indicate early upper airway obstruction.

MANAGEMENT

Critical airway compromise may be present on arrival at the hospital or it may develop subsequently. A major pitfall in managing a patient with smoke inhalation is failing to appreciate that rapid deterioration is possible. The history and physical findings help to determine significant smoke exposure and the potential for clinical deterioration.

When obvious oropharyngeal burns are observed, upper airway injury is almost certain, even if overt injuries are not present. Distal injury may be present and underestimated. Direct evaluation of the upper airway, preferably with fiberoptic endoscopy, is essential for assessing patients at high risk for inhalation airway injury. When evidence of upper airway injury exists, early endotracheal intubation should be performed under controlled circumstances. Because massive fluid resuscitation of the burned patient also contributes to upper airway edema, early intubation may be necessary in the patient with dermal burns. Figure 123–1 describes the clinical effects of smoke exposure and their appropriate treatment. Additional details are found in Chaps. 119–122 and in Antidotes in Brief: Hyperbaric Oxygen; Antidotes in Brief: Methylene Blue; Antidotes in Brief: Sodium and Amyl Nitrite; Antidotes in Brief: Sodium Thiosulfate; and Antidotes in Brief: Hydroxocobalamin.

Pathophysiologic changes in the lung may cause progressive hypoxia over hours to days. Treatment of progressive respiratory failure includes mechanical ventilation, continuous positive airway pressure, positive end-expiratory

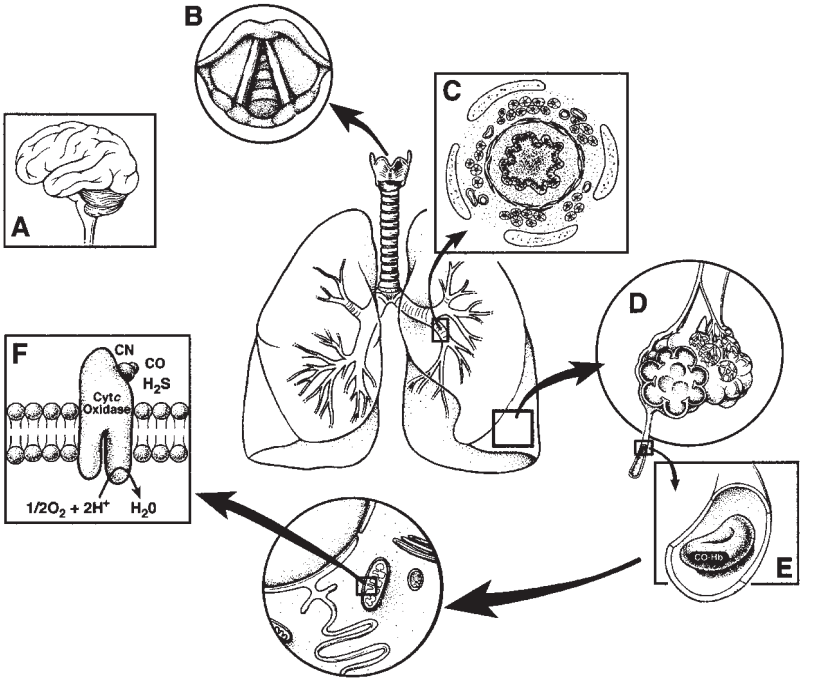

FIG. 123–1. The final common pathway from all pathophysiologic changes that occur in smoke inhalation is hypoxia. All treatments should be focused on improving oxygen delivery and oxygen use. *(continued)*

Pathophysiology	Signs and Symptoms	Management
A) Direct CNS toxic effects	Coma Hypoventilation	Oxygen; Secure unprotected airway
B) Upper airway edema	Hypoxemia; Respiratory distress Stridor Hoarse voice	Oxygen Direct visualization of vocal cords Endotracheal intubation
C) Bronchiolar airway obstruction Mucosal edema Intraluminal debris and casts Inspissated secretions Bronchospasm	Respiratory distress Hypoxemia Wheezes Cough Increased peak airway pressures	Oxygen Removal of debris and secretions Chest physical therapy Frequent airway suctioning Therapeutic bronchoscopy Inhaled β-adrenergic agonists
D) Atelectasis Surfactant destruction Acute Lung Injury (ALI)	Respiratory distress Hypoxemia Crackles Chest radiographic changes	Oxygen Continuous positive airway pressure Mechanical ventilation Positive end-expiratory pressure
E) Impaired oxygen-carrying capacity (carbon monoxide or methemoglobinemia)	CNS depression or seizures Myocardial ischemia Dysrhythmias Metabolic acidosis	Oxygen Consider hyperbaric oxygen Consider methylene blue
F) Impaired oxygen use at tissues (cyanide, hydrogen sulfide, or carbon monoxide)	CNS depression or seizures Myocardial ischemia Dysrhythmias Metabolic acidosis	Oxygen Assure adequate tissue perfusion Consider treating suspected cyanide toxicity with sodium thiosulfate Consider hyperbaric oxygen

FIG. 123–1. *(continued)*

pressure, and vigorous clearing of pulmonary secretions. Frequent airway suctioning, chest physical therapy, and therapeutic bronchoscopy can clear inspissated secretions, plugs, and casts.

Respiratory compromise and other conditions may not be a result of smoke inhalation, but rather a result of trauma or underlying medical problems. Trauma from falls or explosions must be suspected and treatment begun simultaneously with treatment of burns and inhalation injury. Comatose patients should be considered to have other etiologies and should receive naloxone, thiamine, and hypertonic dextrose, as indicated. Rapid removal of soot from skin or eyes may prevent continuing injury. The eyes should be evaluated for corneal burns caused by thermal or irritant chemical injury. Patients with signs of ocular irritation should have their eyes irrigated. Dermal decontamination should be considered to prevent dermal burns from toxin-laden soot adherent to the skin.

Proper management of the victim of smoke inhalation comes from an integrated understanding of burns, trauma, and the multiple toxins generated from combustion. It is essential to consider each element so as to assure an optimal outcome.

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N. Disaster Preparedness

124 Risk Assessment and Risk Communication

Responding to an anxious patient's questions about a potentially toxic exposure requires that the healthcare provider establish a rapport and provide information, instructions, and reassurance. The healthcare provider must be capable of a knowledgeable, compassionate, and well-reasoned response. This chapter focuses on two particular components of this response: risk assessment and risk communication.

RISK ASSESSMENT

Risk assessment is the process of determining the likelihood of toxicity following a perceived exposure. It involves determining the nature and extent of the exposure (xenobiotic, dose, duration, route) and its specific clinical effects, defining an exposure pathway, and assessing the likelihood of effects from the exposure. Although it is generally true that a published body of knowledge can be applied to the risk characterization or assessment, this assessment is often based on incomplete (eg, exact dose) or unpredictable (eg, host factors that modify a response) information. The emotional response to being "poisoned" makes this task even more difficult. Those performing a risk assessment are affected by their own biases and assumptions in the interpretation of their results, as are the people to whom a risk assessment is communicated.

The response of individuals to uncertainty correlates with their affinity for one component of the negative data paradigm: "the absence of evidence of harm" or "evidence of absence of harm." Unfortunately, these converging points on a spectrum of knowledge and research are polarized into two positions. The first position is best summarized as "prove something is harmful before excluding a product with known benefits because of concern about potential, unproven, future adverse effects." The alternative position is often summarized as "where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." The response to uncertain situations is derived from one's belief systems and assumptions about life, justice, and eternity. These underlying worldviews should be explicitly recognized and addressed in a formal risk assessment. Table 124–1 lists the components of a risk assessment.

DIFFERENTIATING PUBLIC HEALTH FROM INDIVIDUAL RISK ASSESSMENT

It is often difficult to translate public health risk assessment done for populations by entities such as the Environmental Protection Agency (EPA) to the individual level. Simplistically, the iterative process of adjusting known non-

TABLE 124–1. Components of a Risk Assessment

Hazard identification
What is the name and amount of the suspected xenobiotic?
In the absence of a specific xenobiotic, what general or use category is suspected?
Exposure pathway
What is the proposed route of exposure?
Is the route of exposure consistent with the nature of the xenobiotic?
Modifying factors
Are there environmental factors that influence the systemic availability of the xenobiotic?
Are there underlying host susceptibility or resistance factors to consider?
Chronic medical conditions?
Possible xenobiotic–drug or other interactions?
Genetic polymorphisms in hepatic or other metabolic pathways?
Toxicity assessment
What organ effects are expected from the identified xenobiotic?
Are existing symptoms consistent with known effects of the presumed xenobiotic?

Adapted with permission from Wallace, K: Banner Health Care, Phoenix, AZ.

cancer adverse exposure outcome limits in an animal model (eg, lowest observed adverse effect level [LOAEL] or no observed adverse effect level [NOAEL]) to a safe level of exposure for all humans (including so-called sensitive subpopulations) has been arbitrarily set at multiplicative factors of 10. These "uncertainty factors" are actually safety factors that can lower exposure limits to amounts as small as 0.001 times the amount demonstrated to cause an adverse effect of interest. Thus when an individual exceeds these limits, the individual remains relatively safe, and is not being exposed to a defined harm.

RISK COMMUNICATION

Risk communication is an exchange of facts and opinions that allows an individual or group to make an informed decision regarding a course of action or treatment. Practically, risk communication is a way of translating incomplete knowledge into a form that will allow for informed decision making. Table 124–2 summarizes the general principles of risk communication.

Effective risk communication must address several questions. Once the best information is obtained about the identification of the xenobiotic and the nature of the exposure, we must convey:

- The likely magnitude of the risk. This includes information on dose-response such as does the reported exposure to a toxic compound approach exposure amounts reported to cause symptoms?
- The urgency of the risk must also be conveyed, along with recommendations to decrease toxicity or ongoing exposure.
- The applicability of a risk characterization might also need to be addressed: Is the animal data applicable to humans? Is the exposure something of concern for an individual?
- Uncertainties of the risk assessment. This could include a "worst-case-scenario" approach to unknown exposures or uncertainties in the quantity of an absorbed dose. The need for continued observation or followup for clin-

TABLE 124–2. Principles of Poison Center Risk Communication

Principles	Applications
1 Accept and involve the public as a partner.	The caller must be involved to obtain the best information possible.
2 Plan carefully and evaluate your efforts.	There is a very short time to establish rapport with the caller; do not increase anxiety by asking irrelevant questions or arguing. Monitor your tone; ask for repetition of key information or recommendations.
3 Listen to the public's specific concerns.	Why did the person call? Was it for information, treatment recommendations, or reassurance? Make sure the underlying reason has been addressed.
4 Be honest, frank, and open.	If there is uncertainty or there are unknowns, indicate that, while providing a workable plan.
5 Work with other credible sources.	Involve medical toxicology backup and other consultants, particularly for questions regarding chronic exposure/effects.
6 Meet the needs of the media.	If calls involve media notification or contact, make sure the critical information is stated frequently, provide a human context, and avoid sensationalism.
7 Speak clearly and with compassion.	Remember that the caller was concerned enough to initiate the contact; make sure the call is completed with a clear plan; provide followup appropriate to the situation.

Modified from Covello V, Allen F: *Seven Cardinal Rules of Risk Communication*. Washington, DC: US Environmental Protection Agency, Office of Policy Analysis, 1988.

ical changes is expressed here. Individual risk tolerance may vary greatly. The same information may be interpreted differently by risk-averse, in contrast to risk-tolerant, people. A variety of comparisons or communication techniques may be used to provide an adequate characterization of risk (see below).

- Options for management. In addition to followup and repeated evaluations by a medical toxicologist, the range of choices, along with their relative benefits or risks, are presented to the individual or group, along with a summary recommendation or opinion from the presenter. This last step is important so as to avoid the impression that "no one is certain as to what is happening or what should be done."

Table 124–3 lists some barriers to effective risk assessment and communication.

INTERPRETING PUBLIC HEALTH CONCERNS FOR THE INDIVIDUAL

Clinicians frequently encounter concerns from individuals at community events, or interact with the media regarding public health-related issues. Often these people are concerned that their symptoms or future health or family health may be adversely impacted by such exposures. Such supposed exposures are usually poorly documented, sometimes are driven by popular media depictions or litigation, and the risk to a caller is virtually impossible to as-

TABLE 124–3. Factors Affecting Appropriate Risk Assessment and Effective Risk Communication

Nature of previous encounters with poison center or healthcare field
Lack of prior patient–healthcare worker relationship
Incomplete data to answer a question
Providing information contrary to "popular understanding" or media representation
Loss of credibility
Individual or cultural differences in perception of risk or applicability of data
Poor comprehension of scientific or statistical principles

certain during a short telephone or personal interaction. In these situations, the individual is best served by referral to a primary care physician with toxicology consultation or directly to a medical toxicology clinic. In such a setting, the data and perceptions can be reviewed completely, and a more appropriate risk assessment communicated. These interactions are very difficult, as they are often emotionally and politically charged.

In general, the communication of, and response to, information is dependent on a preexisting worldview and prevailing circumstances. The same possible outcome will be perceived as more or less severe, based on several factors other than the nature of the outcome itself. Several authors have characterized the perceived tolerance to different risks, stratified by features such as familiarity and personal control (Table 124–4). Unfortunately, there are many factors that affect the characterization of risk other than the facts, as exemplified by the following two composite articles, each describing the same events.

> An unknown assailant (or assailants) has infiltrated the mail delivery system, resulting in severe illness and death throughout the country. Victims include children, healthy adults, and the elderly. Initial symptoms can be nonspecific, but rapidly progressive. If treatment is not begun early, death is a likely result. Anyone who receives regular mail may be at risk. The government has no system in place to detect this threat, and the medical community routinely fails to diagnose the conditions early. The long-ignored public health system is not prepared to deal with the huge burden of preventing illness in those who may have been or will be exposed. Tens of thousands of our citizens are taking prophylactic antibiotics "just in case." If you receive any unusual packages or see collections of powder that don't have an obvious ex-

TABLE 124–4. Factors That Alter the Acceptability of Perceived Risk

More Acceptable	Less Acceptable
Natural	Man-made
Associated with a trusted source	Not associated with a trusted source
Familiar	Exotic
Voluntary	Involuntary
Potentially beneficial	Limited or absent potential benefit
Statistical (low harm likelihood)	Catastrophic (high harm likelihood)
Fairly distributed or shared by all	Unfairly distributed (injustice)
Affects adults	Affects children

Modified from Fischhoff B, Lichtenstein S, Slovic P, Derby SL, Keeney RL: *Acceptable Risk*. Cambridge, MA: Cambridge University Press, 1981.

planation, call the police. If you develop a fever, cough, chest pain, or unusual rash—which may not be painful—seek medical attention at once. Tune in to your local news station for more information on this burgeoning threat to our nation's security.

A small number of individuals in isolated exposure settings developed illnesses following bioterrorism events. Although the most severe form of this disease was previously thought to have a very high mortality rate, most people survive these exposures, particularly with early and proper medical care. For the general population, it is estimated that the risk of exposure is about 1 in 200,000,000. The government developed a case definition and medical experts disseminated information to assist the medical community and public in the early recognition of symptoms and signs that are consistent with this exposure. Prophylactic treatment within days of exposure of those in high-risk professions, such as mail handlers at major postal sorting facilities, prevents illness. Unfortunately, there have been a large number of hoaxes and false alarms about possible terrorist events, and a lot of understandable fear in the community about nonspecific symptoms. For additional information, contact your state health department at 2-1-1 or go to http://www.bt.cdc.gov/agent/anthrax/needtoknow.asp.

Both paragraphs describe the 2001 anthrax bioterrorism events within the United States in which a total of 22 people were sickened or died from anthrax exposure. The first is sensationalistic, imparting a helpless-victim role to the reader, whereas the second provides a framework in which to assess one's personal risk and access to sources of reliable information. As biopreparedness moves from infrastructure and surveillance improvement to planning and response drills, appropriate message development and risk communication to the public becomes increasingly important.

High-quality risk assessment and effective risk communication are the hallmarks of a successful interaction between the public or an individual patient and the healthcare provider. Adherence to general principles of risk assessment include obtaining the best information possible regarding potential exposures, and conveying a risk characterization of the hazard, likelihood of a completed exposure pathway, possible effects, and treatment options that is as complete as possible in an understandable fashion. It is important to clarify the difference between public health standards and individual exposure risks, with an understanding of the many psychosocial issues that influence perception. Information should be provided in a context that allows the individual to prioritize his or her response based on a factual and balanced presentation.

125 Hazmat Incident Response

HAZMAT INCIDENT RESPONSE

A hazardous material (hazmat) can be defined as any xenobiotic capable of harming people, property, or the environment; therefore, the list of hazardous materials is large. A hazardous materials emergency is an uncontrolled or unexpected release of a hazardous material. A hazmat incident response focuses on the care of patients exposed to xenobiotics in the prehospital setting, prepares for multicasualty incidents, and emphasizes patient decontamination, while at the same time trying to prevent contamination of healthcare providers. The general principles of toxicology apply regardless of whether a patient is at a hazmat incident, in a prehospital setting, or in a hospital setting. Although patient-care resources vary among these treatment settings, the fundamental principles of patient care remain the same.

Because the number of hazardous materials is so large, it is efficient to group hazardous materials according to their toxicologic characteristics. Various classification systems have been devised. The International Hazard Classification System (IHCS) is the most commonly used (Table 125–1).

Epidemiology

Data indicate that the majority of hazmat incidents occur at fixed facilities rather than during transportation. The substances most commonly encountered at hazmat incidents vary from one locale to another and are predominately determined by the major industries in a particular area. Although most hazmat incidents involve only one hazardous material, more than one hazardous material can be encountered at a given incident. The vast majority of consequential hazmat incidents are caused by gases, vapors, and aerosols. In one study, four of the five most commonly encountered individual chemicals were ammonia, phosphine, sulfur oxides, and hydrogen sulfide. As expected, inhalation is the most common route of exposure at hazmat incidents, accounting for 76% of exposed patients. Most patient-producing hazmat incidents are multicasualty incidents.

Hazardous Materials and Hazmat Response

Chemical Names and Numbers

Chemical compounds may be known by several names, including the chemical, common, generic, or brand (proprietary) name. The Chemical Abstracts Service (CAS) of the American Chemical Society (ACS) numbers chemicals to overcome the confusion regarding multiple names for a single chemical. The CAS assigns a unique CAS registry number (CAS#) to atoms, molecules, and mixtures. The material safety data sheet (MSDS) describing a product usually lists the chemical name, the CAS#, and the brand name.

Vehicular Placarding: UN Numbers, NA Numbers, and PIN

Substances in each hazard class of the IHCS (Table 125–1) are assigned 4-digit identification numbers, which are known as United Nations (UN), North American (NA), or Product Identification Numbers (PIN) and are displayed on characteristic vehicular placards.

TABLE 125–1. International Hazard Classification System

Class 1: Explosives
- Division 1.1: Mass explosion hazard
- Division 1.2: Projection hazard
- Division 1.3: Predominantly a fire hazard
- Division 1.4: No significant blast hazard
- Division 1.5: Very insensitive explosives
- Division 1.6: Extremely insensitive detonating articles

Class 2: Gases
- Division 2.1: Flammable gases
- Division 2.2: Nonflammable compressed gases
- Division 2.3: Poisonous gases
- Division 2.4: Corrosive gases (Canada)

Class 3: Flammable/combustible liquids

Class 4: Flammable solids
- Division 4.1: Flammable solid
- Division 4.2: Spontaneously combustible materials
- Division 4.3: Dangerous when wet materials

Class 5: Oxidizers and organic peroxides
- Division 5.1: Oxidizers
- Division 5.2: Organic peroxides

Class 6: Poisonous materials and infectious substances
- Division 6.1: Poison materials
- Division 6.2: Infectious substances

Class 7: Radioactive substances

Class 8: Corrosive materials

Class 9: Miscellaneous hazardous materials

National Fire Protection Association 704 System for Fixed-Facility Placarding

Fixed facilities, such as hospitals and laboratories, use a placarding system that is different from the vehicular placarding system. The National Fire Protection Association (NFPA) system uses a diamond-shaped sign that is divided into four color-coded quadrants; red, yellow, white, and blue. This system gives hazmat responders information about the flammability, reactivity, and health effects, as well as other information, such as the water reactivity, oxidizing activity, or radioactivity. The red quadrant on top indicates flammability; the blue quadrant on the left indicates health hazard; the yellow quadrant on the right indicates reactivity; and the white quadrant on the bottom is for other information, such as OXY for an oxidizing product, W for a product that has unusual reactivity with water, and the standard radioactive symbol for radioactive substances. Numbers in the red, blue, and yellow quadrants indicate the degree of hazard: numbers range from 0, which is minimal, to 4, which is severe, and indicate specific levels of hazard.

Substance Identification

Fixed facility placards, vehicular placards, MSDSs, bills of lading, shipping documents, inventory sheets, and verbal information from employees and management are potential sources of information. CHEMTREC is a service of the Chemical Manufacturers Association. It has information about shippers, prod-

ucts, and manufacturers. CHEMTREC can be reached at 1-800-424-9300. The Internet address for CHEMTREC is http://www.chemtrec.org. CHEMTREC provides information 24 hours a day at no charge. A regional poison center is also another valuable source of information. Other information sources include local and state health departments, the American Conference of Governmental and Industrial Hygienists (ACGIH), the Occupational Safety and Health Administration (OSHA), National Institutes of Occupational Safety and Health (NIOSH), Agency for Toxic Substances and Disease Registry (ASTDR), and the Centers for Disease Control and Prevention (CDC).

Even if the exact identity of the toxic material is not known, hazmat responders may be able to classify the hazardous material into one of several major toxicologic classes by identifying a toxic syndrome that allows them to treat the patient and protect themselves and others.

Primary and Secondary Contamination

The state of matter will also help healthcare providers determine whether the hazardous material presents a significant risk of secondary contamination and whether decontamination of the skin and mucous membranes is necessary.

Primary contamination is defined as contamination of people or equipment caused by direct contact with the initial release of a hazardous material by direct contact at its source of release. Primary contamination can occur whether the hazardous material is a solid, a liquid, or a gas.

Secondary contamination is defined as contamination of healthcare personnel or equipment caused by direct contact with a patient or equipment covered with adherent solids or liquids that have been removed from the source of the hazardous material spill.

Water Solubility

The water solubility of a hazardous material determines whether water alone is sufficient for skin decontamination or whether a detergent must also be used.

Vapor Pressure

The vapor pressure (VP) is useful to estimate whether enough of a solid or liquid will be released in the gaseous state to pose an inhalation risk. VP is defined as the quantity of the gaseous state overlying an evaporating liquid or a subliming solid. The lower the VP, the less likely the chemical will volatilize and generate a respirable gas.

Hazmat Scene Control Zones

Scene management is a fundamental feature at a hazmat incident. It is almost always necessary to isolate the scene, deny access to the public and the media, and limit access to emergency response personnel so as to prevent needless contamination. Three control zones are established around a scene and are described either by "temperature," "color," or "explanatory terminology" (Table 125–2).

Personal Protective Equipment

A critical goal of hazmat emergency responders is protecting themselves as well as the public. Safeguarding hazmat responders includes wearing appropriate personal protective equipment (PPE) to prevent exposure to the hazard and preventing injury to the wearer from incorrect use of or malfunction of the PPE equipment. Personal protective equipment can create significant health hazards, including loss of

TABLE 125–2. The Nomenclatures of the Hazmat Control Zones

Temperature Terminology System[a]	Color Terminology System	Explanatory Terminology System
Hot zone	Red zone	Exclusion or restricted zone
Warm zone	Yellow zone	Decontamination or contamination reduction zone
Cold zone	Green zone	Support zone

[a]NIOSH, EPA. Adapted with permission from the Advanced Hazmat Life Support Provider Manual, 2nd ed. Tucson, AZ, Arizona Board of Regents, 2000.

cooling by evaporation, heat stress, physical stress, psychological stress, impaired vision, impaired mobility, and impaired communication. Because of these risks, individuals involved in hazmat emergency response must be trained regarding the appropriate use, decontamination, maintenance, and storage of PPE.

Levels of Protection

The US Environmental Protection Agency (EPA) defines four levels of protection for PPE: A (highest) through D (lowest). The different levels of PPE are designed to provide a choice of PPE, depending on the hazards at a specific hazmat incident (Table 125–3).

Level A PPE is airtight, and the breathing apparatus must be worn under the suit. *Level B* provides the highest level of respiratory protection but less skin protection. *Level C* protection is used when the criteria for using air-purifying respirators are met, and when skin and eye exposures are unlikely. Level C provides skin splash protection, the same as level B; however, level C has a lower level of respiratory protection than either level A or B. *Level D* is comparable to a standard work uniform.

PPE Respiratory Protection

Personnel must be fit-tested before using any respirator. A tiny space between the edge of the respirator and the face of the hazmat responder could permit

TABLE 125–3. Personal Protective Equipment

	Protects Respiratory System from			Protects Skin and Eyes from	
Level[a]	Select Vapors and Aerosols	Gases, Vapors, and Aerosols	Oxygen-Deficient Atmospheres	Liquids and Solids	Gases and Vapors
D					
C	+			+	
B	+	+	+	+	
A	+	+	+	+	+

[a]Definitions: level A, a self-contained breathing apparatus (SCBA) worn under a vapor-protective, fully encapsulated, airtight, chemical-resistant suit; level B, a positive-pressure supplied-air respirator with an escape SCBA worn under a hooded, splash protective, chemical-resistant suit; level C, an air-purifying respirator worn with a hooded, splash protective, chemical-resistant suit; level D: regular work clothing (offers no protection).

exposure to an airborne hazard. Contact lenses cannot be worn with any respiratory protective equipment. Corrective eyeglass lenses must be mounted inside the face mask of the PPE. The only exception to these general rules are the use of hooded, level C, powered air-purifying respirators (PAPRs) that do not require fit testing and allow individuals to wear their own eyeglasses within the hooded PAPR.

Level A PPE mandates use of a self-contained breathing apparatus (SCBA). A supplied-air respirator (SAR) may be used in level B PPE and differs from SCBA in that air is supplied through a line that is connected to a source located away from the contaminated area. One major advantage of SARs over SCBA is that they allow an individual to work for a longer period. An air-purifying respirator (APR) may be used in level C PPE and allows breathing of ambient air after inhalation through a specific purifying canister or filter. There are three basic types of APRs: chemical cartridge, disposable, and powered-air.

Hazmat Incident Response Rules and Standards

OSHA and NFPA have developed, respectively, rules and guidelines regarding hazmat incident response. NFPA 472, "Standard on Professional Competence of Responders to Hazardous Materials Incidents," helps define the minimum skills, knowledge, and standards for training for the following three types of responders.

First Responder at the Awareness Level

First responders at the awareness level could be first on the scene at an emergency incident involving hazardous material. They are expected to recognize the presence of hazardous materials, protect themselves, secure the area, and call for better-trained personnel. They must take a safe position and keep other people from entering the area. They must recognize that the level of mitigation exceeds their training and call for a hazmat response team. Most emergency medical technician (EMT) basic curricula include this level of first-responder training.

First Responder at the Operational Level

These individuals are trained in all competencies of the awareness level and are additionally trained to protect nearby persons, the environment, or exposed property from the effects of hazmat releases. Operational level certified individuals are expected to assume a defensive posture, to control the release from a safe distance, and to keep the hazardous material from spreading. Operational level individuals are trained to perform absorption of liquids, containment of the spill, vapor suppression, and vapor dispersion. They do not operate within the hot zone.

Hazardous Materials Technician

Hazardous materials technicians respond to hazmat releases, or potential releases, for the purpose of controlling the release. They are trained in the use of chemical resistant suits, air monitoring equipment, mitigation techniques, and the interpretation of physical properties of hazardous materials. Technicians are capable of containing an incident, making safe entry into a hazardous environment, determining the appropriate course of action, rescuing victims, and cleaning up or neutralizing the incident so as to return the property to a safe and usable status, if possible. These individuals are trained to operate within the hot zone to mitigate the incident.

Prehospital Hazmat Emergency Response Team

Hazmat responders should identify the entry and exit areas by controlling points for the access corridor (decontamination corridor) from the hot zone, through the warm zone, to the cold zone. This corridor should be upwind, uphill, and upstream from the hot zone, if possible. Hazmat technician entry team members should remove victims from the contaminated hot zone and deliver patients to the inner control point of the access (decontamination) corridor. Hazmat decontamination team members decontaminate patients in the decontamination (access) corridor of the contamination reduction (warm) zone. After decontamination, hazmat responders deliver patients to paramedics in the cold zone.

The primary responsibility of the *prehospital hazmat medical sector* is the protection of the hazmat entry team personnel.

Patient Care Responsibilities of EMS Paramedics at Hazmat Incidents

Emergency medical services (EMS) paramedics who are not part of the hazmat team should remain in the cold zone until properly protected hazmat incident responders arrive, decontaminate, and deliver patients to them for further triage. Initial EMS patient care generally takes place in the patient staging area of the cold zone, including medical management of hazmat victims. Decontamination should not be necessary because EMS paramedics in the cold zone should care only for decontaminated patients or patients who did not initially have skin contamination.

Transportation of patients from the hazmat incident is ultimately under the control of the incident commander, but is usually delegated to the prehospital hazmat medical sector and EMS paramedics in consultation with a base hospital physician. In general, no victim with skin contamination should be transported from the hazmat site without being properly decontaminated.

Emergency Department Responsibilities for Hazmat Victims

It is critical that hospitals be involved with community hazmat planning to ensure that as many hazmat victims as possible are decontaminated in the field before delivery to the hospital. The hospital must have a preestablished protocol by which hospital response teams will decontaminate patients who arrive at the hospital if not previously decontaminated. Hazmat patients who require skin decontamination should be denied entry to the emergency department until decontaminated by an appropriately trained and equipped hazmat response team.

Decontamination

Decontamination has two important functions: altering absorption for the patient and preventing secondary contamination of others. Primary goals at any hazmat incident are protecting emergency responders, preventing secondary contamination, and decreasing morbidity and mortality of hazmat victims. Prompt, adequate skin decontamination is the most important determinant to improve patient outcome with chemical burns. Exposure solely to gases, such as simple asphyxiants, generally requires no skin or mucous membrane decontamination to prevent secondary contamination of others. However, exposure to highly water soluble irritant gases, such as anhydrous ammonia, can cause skin and mucous membrane irritation and chemical burns; these expo-

sures are treated with copious water irrigation. This approach treats the individual patient rather than primarily preventing secondary contamination of healthcare providers.

When the eyes are exposed they should be continuously irrigated with water throughout the patient contact, including transport, if possible. Remember to check for and remove contact lenses. Use of irrigation lenses are the most efficient method to decontaminate a patient's eyes, but this requires using an ocular topical anesthetic such as proparacaine.

Role of the Emergency Physician in Collaboration with the Emergency Department Nursing Staff and Hospital Safety Officer

- Provide prehospital medical control as the base hospital emergency physician, if possible.
- Activate the hospital's disaster plan, initiating the hospital incident command, if indicated.
- Contact the poison center and/or medical toxicologist or, alternatively, call the hospital's chemical spill coordinator or the hospital's radiation control personnel if the substance is believed to be radioactive.
- Decide what procedures should be used in the field for decontamination in conjunction with the poison center and/or medical toxicologist.
- Advise prehospital EMS personnel on precautions and adequate decontamination procedures.
- Decide if field decontamination procedures are adequate with the help of the poison center and/or medical toxicologist.
- Meet the ambulance and decontaminated patients outside of the emergency department and reassess for the adequacy of decontamination before patient entry into the emergency department.
- Deny emergency department entry if a patient with skin contamination has not been decontaminated before arrival in the emergency department, and if necessary, contact dispatch to send a hazmat response team to the emergency department while the patient waits outside the emergency department in an area of limited patient traffic.
- Notify hospital security to provide emergency department security and deny entry of contaminated patients unless the attending emergency physician makes a conscious decision to allow entry after considering the risks and benefits.
- Decide if and how a decontamination room should be used, if necessary and if available.
- Decide if an additional decontamination area should be prepared outside the emergency department and if so, establish the external unit.
- Review current emergency department status and staffing and assign personnel to care for all emergency department patients.
- Call an appropriate level trauma alert if the patient has physical injuries.

126 Chemical Weapons

HISTORY

Recent years have witnessed an enormous resurgence of interest in chemical and biologic weapons (CBW). Although "unconventional" warfare with chemical and biologic agents has been practiced since antiquity, it was not until the 20th century that such weapons have been manufactured and used on a mass scale. In addition to battlefield use, chemical weapons may appeal to terrorist groups, in that the technology and financial outlay required to produce them is much less than for nuclear weapons, while the potential morbidity and mortality remain high (Table 126–1). Biologic warfare agents share many characteristics with chemical agents (Table 126–2) and are discussed in Chap. 127, although the issues common to both chemical and biologic weapons are discussed in this chapter.

The first well-documented intentional use of chemicals as weapons occurred in 429 B.C., when Spartans besieging Athenian cities burned pitch-soaked wood and brimstone to produce sulfurous clouds. Large-scale chemical warfare began in World War I. Germany began producing nerve agents just before World War II. They were later given names such as GA, GB, and GD. In 1952, the British synthesized a more potent nerve agent, which was given to the United States and was named VX. The United States used defoliants and riot-control agents in Vietnam and Laos. Iraq used sulfur mustard, tabun, and soman during its war with Iran, and may have also used cyanide against the Kurds.

More recently, terrorist groups have begun to employ chemical weapons. Sarin was released twice by the Aum Shinrikyo cult in Japan. Cult members have also used VX in assassinations.

GENERAL CONSIDERATIONS

Preparation for CBW Incidents

A rational medical response to CBW events differs from the common response to isolated toxicologic incidents. Healthcare providers must protect themselves and their facilities first, or, ultimately, no one will receive care. The responses to chemical and biologic agents will also differ. Chemical weapons, like conventional explosives, generally produce clinical effects within seconds to hours, making a "scene" or "hot zone" evident. The first responders for a chemical event will be fire and police authorities, hazardous material (hazmat) teams and emergency medical services (EMS). Patients will be brought to local area healthcare facilities and the disease process, although perhaps not the specific diagnosis, will be recognized. With biologic agents, the victims will not all present for care at the same time in the same place. First responders will be local and distant emergency departments and primary care offices, highlighting in these specialties the need for further training of healthcare personnel. Currently, there is no standard curriculum for the training of emergency and other physicians about the health hazards related to nuclear, biologic, and chemical (NBC) weapons, although progress in this regard is underway. Anesthesiologists and critical care specialists, too, are recognizing their lack of formalized training in preparing for chemical mass-casualty incidents.

TABLE 126–1. Unconventional Weapons: Definitions and Acronyms

Chemical warfare	Intentional use of weapons designed to kill, injure, or incapacitate on the basis of toxic or noxious chemical properties
Biologic warfare	Intentional use of microorganisms or toxins derived from living organisms to cause death, disability, or damage in humans, animals, or plants
Terrorism	The unlawful use of force against persons or property to intimidate or coerce a government, the civilian population, or any segment thereof, in furtherance of political or social objectives
CW	Chemical warfare or chemical weapon
BW	Biological warfare or biologic weapon
CBW	Chemical and/or biologic warfare, or weapons
NBC	Nuclear, biologic and/or chemical; usually in reference to weapons
WMD	Weapons of mass destruction; nuclear, radiologic, chemical, and/or biologic weapons intended to produce mass casualties

In preparation for the 1996 Olympic Games in Atlanta, a multidisciplinary task force was assembled to detect, identify, and respond to any CBW threat or release of toxic industrial chemicals. Efforts included stockpiling antibiotics and antidotes, training first responders, enhancing surveillance, and augmenting clinical capabilities. The group correctly suspected that the most likely terrorist event was use of conventional explosives; nevertheless, samples from the Centennial Park explosion were rapidly obtained to exclude dissemination of any CBW agent. Such an intense response to the threat of CBW terrorism would be difficult to maintain for extended periods.

Table 126–3 summarizes the recommendations for healthcare facility domestic preparedness. Communication is always a key issue in disaster management. Preestablished lines of communication and command should be implemented. Outside agencies should also be alerted to CBW incidents, which in the United States should include, at a minimum, the Federal Bureau of Investigation and the Centers for Disease Control and Prevention (Table 126–4).

Decontamination

Decontamination serves two functions: (a) to prevent further absorption and spread of a noxious substance on a given individual and (b) to prevent spread to other persons. Decontamination is critical for some chemical weapons exposures, but is less crucial for biologic agents. Chemical agents that are exclusively gases at normal temperatures and pressures (eg, chlorine, phosgene, and hydrogen cyanide) require only removing the victim from the area of exposure. Experience with sarin suggests that clothing should be removed from victims of nerve agent vapor exposure and placed in airtight receptacles, such as plastic bags. Chemical weapon agents dispersed as liquids present the greatest need for decontamination. Liquid-contaminated clothing must be removed, and if able, victims should remove their own clothing to prevent cross-contamination. Decontamination should be performed as soon as practicable, to prevent progression of disease, and done so outside of healthcare facilities, to prevent contamination of the working environment and secondary casualties. Rapid washing is more important than the solution used. Care should be taken to clean the hair, intertriginous areas, axillae, and groin.

TABLE 126–2. Chemical versus Biologic Weapons: Comparison and Contrast

Similarities
Agents most effectively dispersed in aerosol or vapor forms
Delivery systems frequently similar
Movement of agents highly subject to wind and weather conditions
Appropriate personal protective equipment prevents illness

Differences	Chemical weapons (CW)	Biologic weapons (BW)
• Rate at which attack results in illness	Rapid, usually minutes to hours	Delayed, usually days to weeks
• Identifying release	Easier because of: Rapid effects Possible chemical odor Commercially available chemical detectors	Harder because of: Delayed effects Lack of color, odor, or taste Limited development of real-time detectors
• Agent persistence	Variable Liquids semipersistent to persistent Gases nonpersistent	Generally nonpersistent; most BW degraded by sunlight, heat, desiccation (exception, anthrax spores)
• Victim distribution	Near and downwind from release point	Victims may be widely dispersed by time disease is apparent
• First responders	EMTs, hazmat teams, firefighters, law enforcement officers	Emergency physicians and nurses, primary care practitioners, infectious disease physicians, epidemiologists, public health officials, hospital administrators, laboratory experts (but may be same as CW if release is identified immediately)
• Decontamination	Critically important in most cases	Not needed in delayed presentations; less important for acute exposures
• Medical treatment	Chemical antidotes, supportive care	Vaccines, antibiotics, supportive care
• Patient isolation	Unnecessary after adequate decontamination	Crucial for easily communicable diseases (eg, smallpox, pneumonic plague); however, many BW agents are not easily transmissible

Adapted from Henderson DA: The looming threat of bioterrorism, Science 1999;283:1279–1282.

TABLE 126–3. Recommendations for Healthcare Facility Response to CBW Incidents

- Immediate access to personal protective equipment (PPE) for healthcare providers
- Decontamination facilities that can be made operational within 2–3 minutes
- Triage of victims into those able to decontaminate themselves (decreasing the workload for healthcare providers) and those requiring assistance
- Decontamination facilities permitting simultaneous use by multiple persons and providing some measure of visual privacy
- A brief sign-in process where patients are assigned numbers and given identically numbered plastic bags to contain their clothing and valuables
- Provision of food, water, and psychological support for staff, who may be required to perform for extended periods
- Secondary triage to separate persons requiring immediate medical treatment from those with minor or no apparent injuries who are sent to a holding area for observation
- Providing victims with written information regarding the agent involved, potential short- and long-term effects, recommended treatment, stress reactions, and possible avenues for further assistance
- Careful handling of information released to the media to prevent conflicting or erroneous reports
- Instituting postexposure surveillance studies

TABLE 126–4. CBW Phone Numbers/Contacts

CDC Emergency Preparedness and Response Branch (770) 488-7100
For advice, or to report a suspected or actual event
www.cdc.gov/nceh/emergency

CDC Bioterrorism Preparedness and Response Activity (404) 639-0385
(800)-cdc-info
http://www.bt.cdc.gov

FBI Weapons of Mass Destruction Operations Unit (202) 324-6928
(202) 324-3000 (Public Relations)
http://www.fbi.gov

Department of Justice Domestic Preparedness National Response Hotline
(800) 424-8802
To report a suspected or actual event

CB HelpLine: Office for Domestic Preparedness
(800) 368-6498
Nonemergent planning and information source for civilian emergency responders

CB HotLine: National Response Center
(800) 424-8802
For chemical and biologic weapons emergencies

U.S. Army Medical Research Institute of Infectious Disease (USAMRIID) Hotline
(888) 872-7443 (USA-RIID)
To assist in BW threat assessment, diagnosis, and treatment issues

Commander, USAMRIID
(301) 619-2833 (Phone)
(301) 619-4625 (Fax)
For information or diagnostics, medical management, and vaccines
http://www.USAMRID.army.mil/

Psychological Effects

Either the threat or the actual use of CBW presents unique psychologic stressors. Even among trained persons, a CBW-contaminated environment will produce high stress through the necessity of wearing protective gear, potential exposure to agents, high workload intensity, and interactions with the dead and dying. Approximately 10–20% of participants in military training exercises, where no chance of actual exposure exists, experience moderate to severe psychological symptoms.

Special Populations

Pregnancy does not appear to be a significant factor in the initial treatment of female victims of chemical weapons (CWs). Children have important differences from adults with regard to CW effects and decontamination efforts. Perhaps the most obvious difference is that children breathe at a lower elevation above the ground and at a higher rate than adults. Because nearly all CW gases and vapors are heavier than air, children will be exposed to higher concentrations than adults in the same exposure setting. Children may also be more susceptible to vesicants and nerve agents because they have thinner and more delicate skin, allowing for more systemic absorption and more rapid onset of injury with sulfur mustard. Children have a larger surface-area-to-mass ratio and may be more likely to carry a toxic or fatal dose of CW agent on their skin. Most children will need assistance and supervision during decontamination procedures; keeping a mother or other adult guardian with a child should be helpful with both decontamination and thermoregulation.

Nerve Agents

Nerve agents are extremely potent organic phosphorus cholinesterase inhibitors (Chap. 109). The pathophysiology of nerve agents is essentially identical to that from organic phosphorus, differing only in terms of potency and physical characteristics of the toxins. The resultant toxic syndrome includes the rapid onset of muscarinic (salivation, lacrimation, urination, defecation, GI cramping, emesis [SLUDGE] syndrome) and nicotinic (muscle fasciculation, weakness, paralysis) signs, as well as central effects (loss of consciousness, seizures, respiratory depression).

Treatment of Nerve Agent Exposure

Decontamination

In critically ill patients, antidotal treatment may be necessary before or during the decontamination process; but generally, decontamination should occur before other treatment is instituted.

Atropine

Atropine is the standard anticholinergic antidote for the muscarinic effects of nerve agents. Atropine does not reverse nicotinic effects but does have some central effects and may thus assist in halting seizure activity (see Antidotes in Brief: Atropine). Typically, less than 20 mg is required in the first 24 hours, even in severe cases. Fewer than 20% of moderately ill patients admitted at one hospital for sarin poisoning in Tokyo required more than 2 mg atropine.

Autoinjectors permit rapid IM injections of antidote through protective clothing and are given in the lateral thigh. In general, conscious casualties not in severe distress self-administer 1 kit (2 mg atropine), moderate to severe cases receive 3 kits (6 mg atropine) initially, and all receive additional doses as necessary every 5–10 minutes. In a mass casualty incident, the intravenous atropine supplies of a hospital may be rapidly depleted. Alternative sources include atropine from ambulances, ophthalmic and veterinary preparations, or substituting alternate antimuscarinics, such as glycopyrrolate.

Oximes

The only oxime approved in the Unites States by the FDA is pralidoxime (pyridine-2-aldoxime) chloride, or 2-PAM, a monopyridinium compound (see Antidotes in Brief: Pralidoxime). Oximes should be given in conjunction with atropine, as they are not particularly effective in reversing muscarinic effects when given alone. Oximes are the only antidotes that can reverse the neuromuscular (nicotinic) effects of fasciculations, weakness, and flaccid paralysis.

Anticonvulsants

Severe human nerve agent toxicity rapidly induces seizures, which persist for a few minutes until the onset of flaccid paralysis. Diazepam has beneficial effects beyond other anticonvulsants and simple γ-aminobutyric acid type A ($GABA_A$) channel agonism, including effects on choline transport across the blood–brain barrier and acetylcholine turnover.

Vesicants

Vesicants are agents that cause blistering of skin and mucous membranes.

Sulfur Mustard

Sulfur mustard is a vesicant alkylating compound similar to nitrogen mustards used in chemotherapy. Nineteenth-century scientists described the compound as smelling like mustard, tasting like garlic, and causing blistering of the skin on contact. Mustard vapor is 5.4 times denser than air. Mustard freezes at 57°F (13.9°C), so it is sometimes mixed with other substances, including such CW agents as chloropicrin or Lewisite, to lower the freezing point and permit dispersion as a liquid.

Sulfur mustard is an alkylating agent that crosslinks purine bases in nucleic acids. DNA repair mechanisms are activated, depleting nicotinamide-adenosine dinucleotide (NAD^+), which, in turn, inhibits glycolysis and ultimately leads to cellular necrosis from adenosine triphosphate (ATP) depletion.

Clinical Effects

The organs most commonly affected by mustard are the eyes, skin, and respiratory tract. Incapacitation may be severe in terms of number of lost work days, time for lesions to heal, and increased risk of infection. In contrast, mortality is rather low. Most deaths occur several days after exposure, either from respiratory failure, secondary bacterial pneumonia, or bone marrow suppression.

Dermal exposure produces dose-related injury. After a latent period of 4–12 hours, victims develop erythema that may progress to vesicle and/or bulla formation and skin necrosis. Skin exposure to vapor typically results in first- or second-degree burns, whereas liquid exposure may result in full-thickness burns.

Latency of several hours also occurs following ocular and respiratory tract exposures. Ocular effects include pain, miosis, photophobia, lacrimation, blurred vision, blepharospasm, and corneal damage. Permanent blindness is rare, with recovery generally occurring within a few weeks. Inhalation of mustard results in a chemical tracheobronchitis. Hoarseness, cough, sore throat, and chest pressure are common initial complaints. Bronchospasm and obstruction from sloughed membranes occur in more serious cases, but lung parenchymal damage only occurs in the most severe inhalational exposures. Nausea and vomiting are common within the first few hours. High-dose exposures may also cause bone marrow suppression.

Treatment

Decontamination is essential in treating the sulfur-mustard casualty, even among asymptomatic victims. In addition to previously described decontamination regimens, animal data suggests that topical iodine preparations (eg, povidone-iodine ointment) may be beneficial in decontaminating sulfur mustard from the skin, although human clinical experience is currently lacking. Further treatment is largely supportive and symptomatic. Severe eye injuries may require topical mydriatics, anesthetics, and petroleum jelly to prevent formation of lid synechiae. Respiratory tract injuries are treated with antitussives, inhaled bronchodilators, mucolytics, and oxygen supplementation as needed. Antibiotics should be reserved until there is confirmation of a bacterial pathogen.

Lewisite

Lewisite was developed to avoid some shortcomings in the use of sulfur mustard in World War I. Pure Lewisite is an oily, colorless liquid. Impure preparations are colored from amber to blue-black to black and have the odor of geraniums. Lewisite is more volatile than mustard and is easily hydrolyzed by water and by alkaline aqueous solutions such as sodium hypochlorite. Lewisite toxicity is similar to that of sulfur mustard, resulting in dermal and mucous membrane damage, with conjunctivitis, airway injury, and vesiculation. An important clinical distinction is that Lewisite is immediately painful, whereas initial contact with mustard is not.

The mechanisms of Lewisite toxicity are not completely known but appear to involve glutathione depletion and arsenical interaction with enzyme sulfhydryl groups. Treatment consists of decontamination with copious water and/or dilute hypochlorite solution, supportive care, and dimercaprol (BAL). BAL is given parenterally for systemic toxicity and is also used topically for dermal or ophthalmic injuries.

Phosgene Oxime

Although classified as a vesicant, phosgene oxime does not cause vesiculation of the skin. It is more properly an urticant or "nettle" agent, in that it produces erythema, wheals, and urticaria likened to stinging nettles.

Cyanides (Blood Agents)

Several cyanides have been used as chemical weapons. During World War I, the French used hydrogen cyanide (HCN) and cyanogen chloride (CNCl). The clinical effects and treatment of cyanide toxicity are discussed in Chap. 121.

Pulmonary Agents

Both chlorine and phosgene were used as war gases in World War I. When released on the battlefield, chlorine forms a yellow-green cloud with a distinct pungent odor detectable at levels that are not immediately dangerous. Phosgene is either colorless or seen as a white cloud as a result of atmospheric hydrolysis. Phosgene is reported to smell like grass, sweet newly mown hay, corn, or like moldy hay (Chap. 119 has the clinical details).

Riot Control Agents

Riot control agents are intentionally nonlethal compounds that temporarily disable exposed individuals through intense irritation of exposed mucous membranes and skin. These compounds are also known as lacrimators, irritants, harassing agents, human repellents, and tear gas. CN (chloroacetophenone) has been widely used since World War I. CN is the active ingredient in Chemical Mace. CS (*O*-chlorobenzylidene malononitrile) has largely replaced CN because of its higher potency, lower toxicity, and improved chemical stability. Exposed persons develop burning irritation of the eyes, progressing to conjunctival injection, lacrimation, photophobia, and blepharospasm. Mucous membranes of the upper aerodigestive tracts can also be involved. Inhalation causes chest tightness, cough, sneezing, and increased secretions. Dermal exposure may cause a burning sensation, erythema, or vesiculation, depending on the dose. Victims generally remove themselves from the offensive environment and recover within 15–30 minutes. Deaths from riot-control agents are rare, and typically occur from respiratory tract complications in closed-space exposures where exiting the area is impossible.

Oleoresin capsicum, or pepper spray, is the essential oil derived from pepper plants (*Capsicum anuum* species) which contain a naturally occurring lacrimator. Capsaicin activates heat-dependent nociceptors, explaining why exposures are experienced as "hot." Severe respiratory tract injuries and fatalities are occasionally reported from exposures to these devices.

The primary treatment for all riot control agents is removal from exposure. Contaminated clothing should be removed and placed in airtight bags to prevent secondary exposures. Skin irrigation with copious cold water is used for significant dermal exposures. Symptomatic treatments, such as with topical ophthalmic anesthetics, nebulized bronchodilators, or oral antihistamines and corticosteroids, are indicated as appropriate in more severely affected victims.

Incapacitating Agents

3-Quinuclidinyl benzilate (BZ or QNB) is an antimuscarinic compound that was developed as an incapacitating CW agent. BZ is 25-fold more potent centrally than atropine, with an ID_{50} (dose that incapacitates 50% of those exposed) of about 0.5 mg. Clinical effects are characteristic for anticholinergics, with drowsiness, poor coordination, slowing of thought processes, and progressing to delirium. BZ takes at least 1 hour to produce initial manifestations, peaks at 8 hours, continues to incapacitate for 24 hours, and takes 2–3 days to fully resolve. Ultrapotent opioids may also be used as incapacitating CW agents. In 2002, Russian security forces used a fentanyl derivative (possibly carfentanil or remifentanil) to end a 3-day standoff with terrorists in a Moscow theater where Chechen rebels held more than 800 hostages.

127 Biologic Weapons

Expertise in dealing with biologic weapons (BW) requires specific knowledge from the fields of infectious disease, epidemiology, toxicology, and public health. Biologic and chemical warfare agents share many characteristics in common, including intent of use, some dispersion methods, and initial defense based on adequate personal protective equipment and decontamination (see Tables 126–1 and 126–2). Key differences between biologic and chemical weapons (CW), however involve a greater delay in onset of clinical symptoms after exposure—that is, the incubation period for BW is greater than the latent period for CW—and that decontamination is less crucial for victims exposed to BW than to CW. In addition, a few BW can reproduce in the human host and cause secondary casualties, and disease following exposure to several of these agents can be prevented by the timely administration of prophylactic medications.

Biologic weapons may be bacteria, viruses, or toxins derived from microorganisms. Some fungi are listed as potential BW, although to date, none are known to have been developed into weapons.

HISTORY

Biologic warfare has ancient roots. Missile-type weapons poisoned with natural toxins were used as early as 18,000 years ago. Recent excavation of an Egyptian tomb, from about 2100 B.C., yielded arrows coated with cardioactive steroids and paralytic toxins. During World War I, Germany was the only combatant nation with an active BW program. German operatives infected Allied livestock with anthrax and glanders. Shiro Ishii, a Japanese army doctor, headed an active BW program throughout Japan's war with China and World War II. Several field trials with bubonic plague were performed on Chinese civilians and Russian troops.

Biologic terrorism and the threat of bioterrorism are now recognized as a growing worldwide public health concern. Outbreaks of salmonellosis and anthrax were traced to intentional releases.

GENERAL CONSIDERATIONS

Differences between BW Incidents and Naturally Occurring Outbreaks

Because the clinical effects of BW are delayed, as may be the symptoms, it can be difficult to differentiate intentional BW releases from naturally occurring disease outbreaks. Several epidemiologic criteria are proposed to aid in such determinations, at least several of which should be identifiable in a BW incident (Table 127–1).

Preparation

Providers in emergency departments and primary care medicine must be educated to recognize the signs, symptoms, and clinical progression of diseases caused by BW. Clear identification, isolation, and aggressive treatment early after exposure within the first 24–48 hours make the best—and only—means

TABLE 127–1. Epidemiologic Clues Suggesting Bioweapons Release

- Large epidemic with unusually high morbidity and/or mortality
- Epidemic curve (number of cases versus time) showing an "explosion" of cases, reflecting a point source in time rather than insidious onset
- Tight geographic localization of cases, especially downwind of potential release site
- Predominance of respiratory tract symptoms because most BW agents are contracted by aerosol inhalation
- Simultaneous outbreaks of multiple unusual diseases
- Immunosuppressed and elderly persons more susceptible
- Nonendemic infection ("impossible epidemiology")
- Unseasonal time for endemic infection
- Organisms with unusual antimicrobial resistance patterns, reflecting BW genetic engineering
- Animal casualties from same disease outbreak
- Absence of normal zoonotic disease host
- Low attack rates among persons incidentally working in areas with filtered air supplies or closed ventilation systems, using HEPA masks, or remaining indoors during outdoor exposures
- Delivery vehicle or munitions discovered
- Law enforcement or military intelligence information
- Claim of BW release by belligerent force

of reducing mortality, and in the case of smallpox or plague, of preventing secondary or tertiary cases.

Decontamination

Biologic weapons are most effective when dispersed by aerosol. Shortly after a known or suspected release of bioaerosols, decontamination is a relatively minor concern, because aerosols sized to reach the lower respiratory tract (<5-μm particles) produce little surface contamination. However, simple removal of clothing will eliminate a high proportion of deposited particles, and subsequent showering with soap and water will probably remove 99.99% of any remaining organisms on the skin.

BIOLOGIC WARFARE AGENTS

Bacteria

Anthrax

Anthrax is caused by *Bacillus anthracis*, a Gram-positive spore-forming bacillus found in soil worldwide. *B. anthracis* causes disease primarily in herbivorous animals. Human anthrax cases generally occur in farmers, ranchers, and among workers handling contaminated animal carcasses, hides, wool, hair, and bones.

Clinical Manifestations A few clinically distinct forms of anthrax may occur, depending on the route of exposure. Cutaneous anthrax results from direct inoculation of spores into the skin via abrasions or other wounds and accounts for approximately 95% of endemic (naturally occurring) human cases. Patients develop a painless red macule that vesiculates, ulcerates, and forms a 1–5-cm brown-black eschar surrounded by edema. Most skin lesions heal spontaneously, although 10–20% of untreated patients progress to septicemia and death. Cutaneous anthrax fatalities are uncommon when treated with antibiotic therapy.

Gastrointestinal anthrax results from ingesting insufficiently cooked meat from infected animals. Patients develop nausea, vomiting, fever, abdominal pain, and mucosal ulcers, which can cause GI hemorrhage, perforation, and sepsis. Mortality from gastrointestinal anthrax is at least 50%, even with antibiotic treatment.

Inhalational anthrax results from exposure to aerosolized *B. anthracis* spores. Although this form of anthrax is very rare, it is so closely associated with occupational exposures that it has been called "woolsorter's disease." After an incubation period of 1–6 days, the patient develops fever, malaise, fatigue, nonproductive cough, and mild chest discomfort, which are easily mistaken for viral or community-acquired pneumonias. The initial symptoms may briefly improve for 2–3 days or the patient may abruptly progress to severe respiratory distress with dyspnea, diaphoresis, stridor, and cyanosis. Bacteremia, shock, metastatic infection such as meningitis, which occurs in approximately 50% of cases, and death may follow within 24–36 hours.

Treatment The primary antibiotics recommended to treat anthrax are ciprofloxacin and doxycycline. In a mass-casualty setting or for postexposure prophylaxis, adults should be treated with ciprofloxacin 500 mg PO every 12 hours. Alternate therapies are doxycycline 100 mg PO every 12 hours or amoxicillin 500 mg PO every 8 hours if the anthrax strain is proven susceptible. The recommended duration of therapy is 60 days. Children can also be treated with ciprofloxacin (15 mg/kg; maximum 500 mg/dose) or amoxicillin (80 mg/kg/d divided every 8 hours; maximum 500 mg/dose).

Inhalational anthrax should be treated initially with intravenous ciprofloxacin 400 mg IV or doxycycline 100 mg IV every 12 hours, along with one or two additional antibiotics with in vitro activity against anthrax (eg, rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin). Children should be given ciprofloxacin 10 mg/kg IV (max 400 mg/dose) or doxycycline 2.2 mg/kg IV (max 100 mg/dose) and additional antibiotics as above.

Plague

Yersinia pestis is a Gram-negative bacillus responsible for more than 200 million human deaths and three major pandemics in recorded history. Naturally occurring plague is transmitted by flea vectors from rodent hosts, or by respiratory droplets from infected animals or humans. Plague is a particularly frightening BW agent because it can cause a communicable form of the disease. Antibiotics must be initiated early after exposure because once symptoms develop, mortality is extremely high.

Clinical Presentation Plague occurs in three clinical forms: bubonic, septicemic, and pneumonic. Bubonic plague has an incubation period of 2–10 days followed by fever, malaise, and painful, enlarged, regional lymph nodes called buboes. In the United States, 85–90% of human plague patients have the bubonic form, 10–15% have a primary septicemic form without lymphadenopathy, and approximately 1% present with pneumonic plague. Secondary septicemia occurs in 23% of patients presenting with bubonic plague. Various skin lesions at the site of inoculation (pustules, vesicles, eschars, or papules) occur in some patients, while the petechiae and ecchymoses that occur in advanced cases may resemble meningococcemia. Distal gangrene from small artery thrombosis may occur, explaining why plague pandemics are sometimes called "The Black Death." If left untreated, bubonic plague carries a 60% mortality rate.

Pneumonic plague is an infection of the lungs with *Y. pestis*. Between 5–15% of bubonic plague patients develop secondary pneumonic plague through septicemic spread of the organism. The incubation period of pneumonic plague after inhalation is 2–3 days. The onset of disease is acute and often fulminant. Patients develop fever, malaise, and cough productive of bloody sputum, rapidly progressing to dyspnea, stridor, cyanosis, and cardiorespiratory collapse. Plague pneumonia is almost always fatal unless treatment is begun with 24 hours of symptom onset.

Diagnosis and Treatment Plague can be diagnosed by various staining techniques, immunologic studies, or by culturing the organism from blood, sputum, or lymph node aspirates. Antibiotic treatment options are similar to those for anthrax. In a mass-casualty setting or for postexposure prophylaxis, adults are treated with doxycycline 100 mg PO twice daily or ciprofloxacin 500 mg PO twice daily. Children receive doxycycline 2.2 mg/kg or ciprofloxacin 20 mg/kg, up to a maximum of the adult doses. Chloramphenicol 25 mg/kg PO 4 times daily is an alternative. The duration of treatment is 7 days for postexposure prophylaxis, and 10 days for mass-casualty incidents. Patients with pneumonic plague need to be isolated to prevent secondary cases.

Tularemia

Tularemia occurs naturally as a zoonotic disease spread by bloodsucking arthropods or by direct contact with infected animal material. Tularemia in humans may occur in ulceroglandular or typhoidal forms, depending on the route of exposure. Ulceroglandular tularemia is more common, occurring after skin or mucous membrane exposure to infected animal blood or tissues. Patients develop a local ulcer with associated lymphadenopathy, fever, chills, headache, and malaise. Typhoidal tularemia presents with fever, prostration, and weight loss without adenopathy.

Antibiotic treatment options are again similar to those for anthrax and plague. In mass-casualty settings, or for postexposure prophylaxis, adults are treated with doxycycline 100 mg twice daily or ciprofloxacin 500 mg orally twice daily for 14 days; pediatric dosing for doxycycline is 2.2 mg/kg or ciprofloxacin 15 mg/kg (maximum = adult dose) twice daily. When dealing with a limited number of casualties, the preferred antibiotics are streptomycin 1 g IM twice daily or gentamicin 5 mg/kg IM/IV once daily.

Brucellosis

Brucellosis has the potential to be used as an incapacitating BW, as it causes disease with low mortality but significant morbidity. Brucellae (*Brucella melitensis, abortus, suis*, and *canis*) cause disease in ruminant livestock. Humans develop brucellosis by ingesting contaminated meat and dairy products or by aerosol transmission from infected animals. Brucellosis commonly presents with nonspecific symptoms such as fever, chills, and malaise, with either an acute or insidious onset. Diagnosis is made by serologic methods or culture. Because single-drug treatment often results in relapse, combined therapy is indicated. Treatments of choice (adult doses) are doxycycline 200 mg/d orally plus rifampin 600–900 mg/d orally for 6 weeks, or doxycycline 200 mg/d orally for 6 weeks with either streptomycin 15 mg/kg twice daily IM or gentamicin 1.5 mg/kg IM q8h for the first 10 days.

Q Fever

Q fever occurs naturally as a self-limited febrile, zoonotic disease contracted from domestic livestock. Q fever is now known to be caused by *Coxiella bur-*

netti, a unique rickettsialike organism that can persist on inanimate objects for weeks to months and can cause clinical disease with the inhalation of only a single organism. After a 10–40 day incubation period, Q fever manifests as an undifferentiated febrile illness, with headache, fatigue, and myalgia. Patchy pulmonary infiltrates on chest radiography that resemble viral or atypical bacterial pneumonia occur in 50% of cases, although only half of these patients have cough and even fewer have pleuritic chest pain. Tetracyclines are the mainstay of therapy, and either tetracycline 500 mg PO q6h or doxycycline 100 mg PO q12h should be given for 5–7 days.

Viruses

Smallpox

Smallpox is caused by the variola virus, a large DNA orthopoxvirus with a host range limited to humans. Prior to global World Health Organization (WHO) efforts to eradicate naturally occurring smallpox by immunization, recurrent epidemics were common and the disease carried roughly a 30% fatality rate in unvaccinated populations. Smallpox is highly contagious. Outbreaks during the 1960s and 1970s in Europe often resulted in 10–20 secondary cases per index case. In 1980, the United Nations World Health Organization certified that smallpox had been eradicated from the world.

The Soviet Union is known to have weaponized smallpox, and the United States and possibly other countries are believed to maintain stocks of variola virus. Smallpox vaccination for military personnel was reinstated in 2002 and was made available for some civilians in 2003.

Transmission of smallpox typically occurs through inhalation of droplets or aerosols, but may also occur through contaminated fomites. The infectious dose is unknown, but is probably only a few virions. After a 12–14-day incubation period, the patient develops fever, malaise, and prostration with headache and backache. Oropharyngeal lesions appear, shedding virus into the saliva. Two to 3 days after the onset of fever, a papular rash develops on the face and spreads to the extremities. The fever continues while the rash becomes vesicular and then pustular.

Vaccination before exposure, or within 2–3 days after exposure, provides almost complete protection against smallpox. The disease most likely to be confused with smallpox is chickenpox (varicella). The lesions of smallpox should all appear at the same stage of development, whereas chickenpox lesions occur at varying stages. Smallpox lesions tend to be found in a centrifugal distribution (face and distal extremities), whereas chickenpox lesions are more centripetal and tend to appear first on the trunk. Two antiviral drugs commercially available in the United States, cidofovir and ribavirin, are effective in vitro against variola.

Even a single case of smallpox should be considered a potential international health emergency and immediately reported to the appropriate public health authorities.

Viral Hemorrhagic Fevers

Several taxonomically diverse RNA viruses produce acute febrile illnesses characterized by malaise, prostration, and increased vascular permeability that can result in bleeding manifestations in the more severely affected patients. Viral hemorrhagic fevers are all highly infectious by the aerosol route, making them candidates for use as BW. These agents include the viruses

causing Lassa fever, dengue, yellow fever, Crimean-Congo hemorrhagic fever, and the Marburg, Ebola, and Hanta viruses. Ribavirin has been used for some viral hemorrhagic fevers, but supportive care is the mainstay of therapy.

Toxins

Several toxins derived from bacteria, plants, fungi, and algae could theoretically be used as BW if produced in sufficient quantities. Because of their high potency, only small amounts of these agents would be needed to kill or incapacitate exposed victims. Fortunately, obstacles in manufacturing weaponizable amounts limits the number of toxins that are practical for use as BW (Chaps. 46 and 114).

Staphylococcal Enterotoxin B

Staphylococcal enterotoxin B (SEB) is one of seven enterotoxins produced by *Staphylococcus aureus*. SEB is recognized as a "superantigen" because of its profound activation of the immune system upon exposure even to minute quantities. As a BW, SEB could be ingested through contaminated food or water, resulting in acute gastroenteritis identical to classic staphylococcal food poisoning. If inhaled as an aerosol, SEB produces fever, myalgia, and a pneumonitis after a 3–12-hour latent period. SEB inhalation can be fatal, but more often would simply be incapacitating for several days to weeks. Treatment is supportive.

Trichothecene Mycotoxins

The trichothecene mycotoxins are low-molecular-weight (250–500 daltons) nonvolatile compounds produced by filamentous fungi (molds) of various genera, including *Fusarium*, *Myrothecium*, *Trichoderma*, and *Stachybotrys*. Trichothecene mycotoxins are unusual among potential BW agents in that toxicity can occur with exposure to intact skin. Naturally occurring trichothecene toxicity results from ingesting contaminated grains or by inhaling toxin aerosolized from contaminated hay or cotton. Outbreaks of ingested trichothecene toxins result in a clinical syndrome called alimentary toxic aleukia, characterized by gastroenteritis, fevers, chills, bone marrow suppression with granulocytopenia, and secondary sepsis—a syndrome similar to acute radiation poisoning.

128 Radiation

Over the last 100 years, radiation injuries and the nature of radiation itself have been vigorously studied as a result of its expanding role in our society. Today, radionuclides are used for a variety of medical and nonmedical purposes, ranging from detecting smoke and diagnostic testing to powering spacecraft. Although useful, radionuclides can present a danger to humans, both through their metallic nature and through the process of radioactive decay. This ionizing radiation may cause injury to multiple cellular structures and critical molecules, such as DNA, resulting in mutations, neoplasms, or cell death. The types of radiation, their sources, and the mechanisms by which they pose a health risk are the subjects of the following discussion.

HISTORICAL EXPOSURES

Radiation became a concern for scientists as a toxin only a year following the discovery of X-rays by Wilhelm Roentgen in 1895. Soon after, Thomas Edison reported corneal injuries in several of his workers conducting experiments using his newly invented X-ray generator. In 1915, the British Roentgen Society, recognizing the potential hazards of radiation, proposed standards for radiation protection of workers, which included shielding, restricted work hours, and medical examinations. The 1917 opening of the Radium Luminous Materials Corporation in Orange, NJ, represented the first of several companies to profit from the novelty and popularity of radium's bluish glow. By 1927, about 100 employees died from osteosarcoma of the jaw and brain tumors, and developed other noncancerous lesions of the mouth, all related to radium exposure. The only occasion a nuclear bomb was used against a human population occurred in August 1945, when the United States dropped two bombs—one on Hiroshima and one on Nagasaki, Japan. Estimates of dead and injured for both cities are well over 200,000. Although many nuclear reactor incidents occur around the world, the most serious occurred at Chernobyl in Ukraine in 1986. Over the first 10 days following the incident, a cloud carrying radioactive material (predominantly ^{131}I and ^{137}Cs) spread to the Baltic States, Scandinavia, and Europe. In addition to the 31 people who died of acute radiation sickness (ARS) in the first few weeks following the event, nearly 250 others in the surrounding area were hospitalized, and an unknown number will suffer other long-term sequelae.

THE PRINCIPLES OF RADIOACTIVITY

Radiation is defined as energy sent out in the form of waves or particles. Despite the strong nuclear force that holds the basic building blocks of atoms together, many isotopes are unstable. Several other forces, most notably the electroweak force, may tip the balance toward instability and an isotope will transform. This process may be intentional, as with the criticality events in a nuclear reactor or nuclear bomb, but mainly occurs spontaneously in nature as the process called radioactive decay.

Radioactive Decay

Unstable nuclei decay or transform into more stable nuclei (daughters) via the emission of various particles or energy. Radioactive decay occurs through

five mechanisms: emission of γ rays, α particles, β particles, positrons, and capture of an electron. It is the emission of these various particles that makes radioactive decay dangerous because these particles form ionizing radiation. The half-life ($t_{1/2}$), a term first used by Ernest Rutherford in 1904, is the period of time it takes for a radioisotope to lose half of its radioactivity. Table 128–1 lists the physical properties of common radioisotopes.

Photons are massless particles that travel at the speed of light and mediate electromagnetic radiation. Depending on the energy of the particles, and, therefore, their wavelength, the radiation has different names. Radiation having the lowest energy and the longest wavelength are called radio waves. As photons become more energetic and have shorter wavelengths, they are called, sequentially, microwaves, heat or infrared, visible light, and ultraviolet rays. γ Rays and x-rays have greater energy than ultraviolet rays and can penetrate deeply into the body, which makes them both deadly and beneficial as radiation therapy.

γ Rays and x-rays are the same and are only distinguishable by their source. γ Radiation is emitted by unstable atomic nuclei in the process of radioactive decay. X-rays come from atomic processes outside the nucleus. For example, an x-ray machine generates x-rays by accelerating electrons through a large voltage and colliding them into a heavy metal target. X-rays and γ rays may have the same energy. Once an x-ray and γ ray of the same energy leave their respective sources they cannot be distinguished from one another. Because of their nature, high-energy γ rays and x-rays can penetrate several feet of insulating concrete.

β *Particles* are also called electrons. Positrons, positively charged electrons, may also be emitted during decay processes. Because of their mass, electrons have less penetration than γ radiation, but may still pass several centimeters into human skin. α *Particles* are helium nuclei (2 protons and 2 neutrons) stripped of their electrons. These particles are the most easily shielded of the emitted particles mentioned and are stopped by a piece of paper, skin, or clothing. Like β particles, α particles principally cause health effects only when they are incorpo-

TABLE 128–1. Physical Properties of Common Radioisotopes

Isotope	Half-Life	Mode of Decay	Decay Energy (MeV)[a]
^{47}Ca	4.53 days	β^-	1.979
^{14}C	5730 yrs	β^-	0.156
^{137}Cs	30.23 yrs	β^-	1.176
^{51}Cr	27.8 days	electron capture	0.752
^{57}Co	270 days	electron capture	0.837
^{67}Cu	61.8 hrs	β^-	0.576
^{3}H	12.26 yrs	β^-	0.02
^{123}I	13.3 hrs	electron capture	1.4
^{131}I	8 days	β^-	0.970
^{40}K	1.28×10^9 yrs	β^-/β^+ electron capture	1.35/1.505
^{32}P	14.3 days	β^-	1.710
^{210}Po	138.4 days	α	5.41
^{222}Rn	3.8 days	α	5.587
^{85}Sr	64 days	electron capture	1.11
^{201}Tl	73 hrs	electron capture	0.41
^{238}U	4.51×10^9 yrs	α	4.268
^{133}Xe	5.27 days	β^-	0.427

[a]MeV = mega-electron volts.

rated. However, because of their very high linear energy transfer (see below), the effects of incorporated α or β particles can be devestating. This effect is best highlighted by the case of Alexander Litvinenko who died in 2006 after being poisoned with polonium-210, an α emmiter. *Neutrons* are primarily released from nuclear fission. The natural decay of radionuclides does not include emission of neutrons. When neutrons are stopped or captured they can cause a previously stable atom to become radioactive. *Cosmic rays* are streams of electrons, protons, and α particles thought to emanate from stars and supernovas.

Ionizing Radiation versus Nonionizing Radiation

Ionizing radiation refers to any radiation with sufficient energy to disrupt an atom or molecule with which it impacts. An electron is removed or some other decay process occurs, leaving behind a changed atom. Depending on the specifics of the interaction, these atoms may now be ionized or highly reactive free radicals. For a source of radiation to pose a threat to tissue, the ionizing particle must be placed in close proximity to vital components of tissue that can sustain damage.

Nonionizing radiation spans a wide spectrum of electromagnetic radiation frequencies. Generally, nonionizing radiation consists of relatively low-energy photons and is used safely in cell phone and television signal transmission, radar, microwaves, and magnetic fields that emanate from high-voltage electricity and metal detectors.

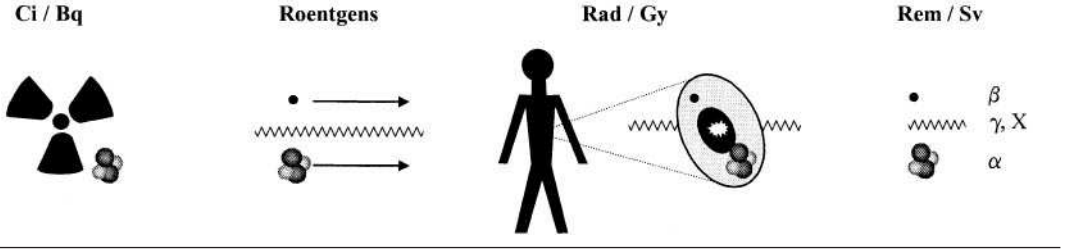
Figure 128–1 illustrates the relationships between common units of measure.

Irradiation, Contamination, and Incorporation

An object that is irradiated is exposed to ionizing radiation. The risk of tissue damage depends on the total amount of radiation and the tissue type because different tissue types have their own intrinsic resistance to radiation damage. Unless exposed to neutrons, an irradiated object does not become radioactive itself. Contamination occurs when a radioactive substance covers an object completely or in part. The source of radiation is the nuclide undergoing its normal decay process, and the individual is exposed to particles such as those mentioned in Table 128–1. The risk for tissue damage from the radiation particles is usually quite low, assuming that the contamination is detected and appropriate measures for decontamination are instituted. Incorporation occurs when a radionuclide is incorporated into a patient's body tissue. It generally follows exposure via the inhalational, enteral, or parenteral route, but may occur via any route that permits a radionuclide to enter the body. Depending on the dose and type of radionuclide, incorporation may lead to tissue damage, as was the situation for many people following the event at Chernobyl.

EPIDEMIOLOGY

Everyone is exposed to radiation in one form or another each day (Table 128–2). Terrestrial sources of radiation originate from radionuclides in the crust of the earth that move into the air and water. Radon, a radioactive inert gas, accounts for most of the human exposure to radiation from natural sources. This gas, a natural decay product of uranium and thorium, enters homes and other buildings from the building materials themselves or through microscopic cracks in the structures of the building. With a relatively short half-life of 3.82 days, ^{222}Rn only poses a health risk if decay occurs while in the respiratory space and deposits on respiratory tissue as one of its daughter isotopes, which are solids. These radon daughters emit α particles as they decay and are the principal causes of



The amount of radioactivity in a radionuclide can be described either by the number of disintegrations per second, the becquerel (Bq), or by comparing the number of disintegrations to that of 1 g of radium, the curie (Ci). One curie equals 3.7×10^{10} disintegrations per second.	Ionizing radiation released during radioactive decay travels in all directions. When it ionizes the air surrounding a source, an electrostatic charge is produced. This ionization is quantified by the roentgen (R), which is an indirect measure of the amount of radiation.	Most γ and x-rays pass through tissue without being absorbed. The particles and the fraction of the rays that are absorbed by tissue can cause cellular damage. This fraction is measured in radiation absorbed dose (rads) or gray (Gy). One Gy equals 100 rad.	For a given energy, larger particles and higher energy rays cause more damage when absorbed by tissue than smaller particles. To predict the degree of damage that a given particle will cause, the dose in rad or Gy is multiplied by the particle-specific biological effectiveness coefficient (Q) to calculate rem or Sv, respectively. One Sv equals 100 rem.

FIG. 128–1. The definitions associated with radiation. Both curie (Ci) and becquerel (Bq) describe a quantity of radionuclide in terms of the number of disintegrations rather than mass. Roentgens describes the amount of air ionized by either gamma (γ) or x-rays, which indirectly quantifies the amount of radiation in the air around a source. Rad and gray (Gy) describe the fraction of radiation that actually interacts with cellular material and potentially causes injury. Roentgen equivalent man (Rem) and sievert (Sv) calculate the effective dose, taking into account the different particles. For example, a 100-keV alpha (α) particle causes more damage to cellular material than does a 100-keV beta (β) particle.

TABLE 128–2. Average Effective Annual Ionizing Radiation Dose Equivalent in the United States

Source	Dose[a]	
	mSv[b]	%
Natural		
Cosmic	0.27	8
Internal	0.39	11
Radon[c]	2.0	55
Terrestrial	0.28	8
Subtotal	**2.94**	**82**
Artificial		
Consumer products	0.10	3
Nuclear medicine	0.14	4
Occupational	<0.01	<0.3
X-ray diagnostic imaging	0.39	11
Subtotal	**0.63**	**18**
Total	**3.6**	**100**

[a]All doses are averages and contain some variability within the measurement.
[b]mSv = millisieverts.
[c]Average effective dose to bronchial epithelium.

the associated increased incidence of lung cancer in those exposed to radon. Artificial sources of radiation can be found in many consumer products and in many different industries (Table 128–3). Medical procedures also account for substantial annual exposure to artificial radiation for patients. Various medical scans use radioactive nuclides to study various disease processes (Table 128–4).

PATHOPHYSIOLOGY

Ionizing radiation causes damage to tissue by several mechanisms depending on its energy. Radiation with high linear energy transfer (LET) predominantly causes direct damage, which is when incoming radiation impacts a target molecule directly. This occurs because high LET radiation, such as an α particle, has a high statistical probability of impacting an important molecule, such as DNA. If this occurs, a mutation may arise, which may then result in alteration of a germ line, development of a neoplasm, or cell death. The risk of these consequences overall, however, is low because of the relative paucity of DNA within a cell and the even smaller percentage of active DNA within a given cell. Low LET radiation, x-rays, γ rays, and fast electrons predominantly cause indirect damage. At this energy, the average separation between ionization events coincides with the diameter of the DNA helix and allows for the greatest probability of double-strand breaks, which is the basis for most biologic effects.

Indirectly, radiation impacts a molecule and creates a reactive species, which then chemically reacts with organic molecules in cells, altering their structure or function. These radiation-induced ions are quite unstable, however, and usually convert to free radicals. Most importantly, radiation may impact a water molecule, which is in great abundance, to generate a hydroxyl radical (OH•).

Although any molecule may be damaged in a variety of ways that may lead to cell injury of varying severity, double-stranded breaks in DNA are the type of damage most likely to cause chromosomal aberrations or cell death. The

TABLE 128–3. Uses of Radioisotopes

^{241}Americium	Used in smoke detectors, to measure lead concentrations in paint, steel, and paper production
^{109}Cadmium	Analyze metal alloys
^{47}Calcium	Biomedical research of cell function and bone formation
^{252}Californium	Inspect luggage for explosives, gauge moisture content of soil and silo materials
^{14}Carbon	Pharmaceutical research, radiometric dating
^{137}Cesium	Measure dosages of radioactive pharmaceuticals, oil industry to measure flow in pipelines
^{51}Chromium	Red blood cell survival studies
^{57}Cobalt	Nuclear medicine
^{67}Copper	Chemotherapy
^{244}Curium	Mining industry
^{123}Iodine	Diagnosis of thyroid disorders
^{129}Iodine	Used to check some radioactivity counters in vitro diagnostic testing
^{131}Iodine	Treatment of thyroid disorders
^{192}Iridium	Test the integrity of pipeline welds, boilers, and aircraft parts
^{55}Iron	Analyze electroplating solutions
^{85}Krypton	Indicator lights, textile industry
^{63}Nickel	Detect explosives, voltage regulators, surge protectors
^{32}Phosphorus	Molecular biology and genetics research
^{238}Plutonium	Power source for NASA spacecraft
^{210}Polonium	Photographic film production, static reduction
^{147}Promethium	Thermostats, textile industry
^{226}Radium	Lightning rods
^{75}Selenium	Protein studies
^{24}Sodium	Industrial pipelines integrity
^{85}Strontium	Study bone formation and metabolism
^{99}Technetium	Nuclear medicine
^{201}Thallium	Cardiac imaging
^{232}Thoriated tungsten	Electric arc welding
^{229}Thorium	Fluorescent lights
^{230}Thorium	Coloring and fluorescence in colored glazes and glassware
^{3}Tritium	Basic science and pharmaceutical studies, for self-luminous signs, luminous dials, gauges and wrist watches, luminous paint
^{234}Uranium	Dental fixtures
^{235}Uranium	Fuel for nuclear power plants and naval nuclear propulsion systems, fluorescent glassware, colored glazes, and wall tiles
^{133}Xenon	Nuclear medicine

radiosensitivity of the cell is directly related to its rate of proliferation and inversely related to its degree of differentiation. Thousands of these types of lesions occur daily in the human body from natural environmental radiation. For this reason, there are several mechanisms that protect and repair damage that may result from either direct or indirect means of radiation damage. It is estimated that up to 90% of all chromosomal breaks heal by adhesion in a process known as "restitution."

TABLE 128–4. Diagnostic Imaging Procedures: The Type and Amount of Radionuclide or Radiation

Test	Radionuclide	Amount
Whole-body bone scan	^{99}Tc	25mCi (9.25×10^8Bq)
Radionuclide cerebral angiogram	^{99}Tc-DTPA	15mCi (5.55×10^8Bq)
Cardiac ejection scan (MUGA)	$^{99}TcO_4$	20mCi (7.4×10^8Bq)
DISIDA/hepatobiliary scan	^{99}Tc-DISIDA	5mCi (18.5×10^7Bq)
Ventilation–perfusion scan	^{133}Xe	10mCi (37×10^7Bq)
	^{99}Tc	4mCi (14.8×10^7Bq)
Thyroid scan	^{123}I	0.2mCi (0.74×10^7Bq)
Myocardial perfusion scan (exercise)	^{201}Tl	3mCi (11.1×10^7Bq)
	^{99}Tc	20mCi (7.4×10^8Bq)
Strontium therapy	^{89}Sr	4mCi (14.8×10^7Bq)
Venogram	^{99}Tc	20mCi (7.4×10^8Bq)
Chest radiograph	60 mrad or 0.06 mGy in a collimated field[a]	
Abdominal radiograph	100–1500 mrad or 1–5 mGy in a collimated field	
CT–head	1–2 rads or 0.01–0.02 Gy per slice[b]	
CT–body	1 rad or 0.01 Gy per slice[b]	

[a]Collimation is the act of restricting the size of the useful X-ray field to the region of clinical interest. These skin-entry doses are approximations dependent on equipment and technique.
[b]The dose per each examination is about the same as the dose per slice and not the sum of the slices.

STOCHASTIC VERSUS DETERMINISTIC EFFECTS OF RADIATION

The radiation damage just described has two consequential results: it kills cells or it alters cells and causes cancer. Injuries that do not require a threshold limit to be exceeded include mutagenic and carcinogenic changes to individual cells where DNA is the critical and ultimate target. This is the stochastic effect of radiation. Theoretically, there is no dose of radiation too small to have the potential of causing cancer in an exposed individual.

Deterministic effects of radiation usually follow a large whole-body exposure. In terms of cell death, a relatively large number of cells of an organ system must be killed before an effect becomes clinically evident. This number of killed cells constitutes a threshold limit that must be exceeded, and this is what is known as the deterministic, or nonstochastic, effects of radiation.

ACUTE RADIATION SYNDROME (ARS)

Understanding the features of ARS is essential for managing a patient who is exposed to massive whole-body irradiation, generally considered to be 1 Gy (250 times the average annual exposure) or more. The ARS syndrome involves a sequence of events that varies with the severity of the exposure. Generally, more severe exposures lead to more rapid onset of symptoms and more severe clinical features. There are four classic clinical stages described, which begin with the early prodromal stage of nausea and vomiting. Although the time to onset postexposure is inversely proportional to the dose received, the duration of the prodromal phase is directly proportional to the dose. That is, the greater the dose received, the more rapid the onset of symptoms, and the longer their duration, unless death occurs rapidly. The latent period follows next as an apparent improvement of symptoms during which

time the patient appears to have recovered and has no clinically apparent difficulties. The duration of this stage is inversely related to dose and may last from several days to several weeks. The third stage usually begins in the third to fifth week after exposure and consists of manifest illness described below. If one survives this stage, recovery, the fourth stage, is likely, but may take weeks to months before it is completed.

The cerebrovascular syndrome describes the manifestations of injury to the central nervous system following massive irradiation. This syndrome, following exposure to doses of about 15–20 Gy or greater, is characterized by rapid or immediate onset of fever, ataxia, loss of motor control, apathy, lethargy, cardiovascular shock, and seizures. The gastrointestinal (GI) syndrome begins following an exposure to about 6 Gy or more where there is gastrointestinal mucosal cell injury and death. Symptoms include anorexia, nausea, vomiting, and diarrhea. As the mucosal lining is sloughed, there is persistent bloody diarrhea, hypersecretion of cellular fluids into the lumen, and a loss of peristalsis, which may progress to abdominal distension and dehydration. Destruction of the mucosal lining allows for colonization by enteric organisms with ensuing sepsis. The hematologic changes that occur following an exposure to about 1 Gy or greater are called the hematopoietic syndrome. Hematopoietic stem cells are highly radiosensitive, in contrast to the more mature erythrocytes and platelets. Lymphocytes are also radiosensitive and can die quickly from cell lysis following an exposure. In addition to stem cell death and white cell depletion with immunodeficiency, platelets are consumed in gingival and gastrointestinal microhemorrhages. The main effect of radiation-induced hematopoietic syndrome is pancytopenia leading to death from sepsis complicated by hemorrhage. A lymphocyte nadir typically occurs 8–30 days postexposure.

DOSE ESTIMATION

Determining the dose received by an individual who was irradiated is important in providing appropriate therapy and establishing a prognosis. However, estimating the dose received is difficult for a number of reasons, such as the absence of a radiation-monitoring device, exposure to radiation of mixed form (such as γ and neutron radiation), and partial shielding of various body parts. The broad ranges of radiation dose that correlate with lymphocyte count are described in the classic Andrews nomogram of 1965 (Fig. 128–2).

The gold standard for biodosimetry are chromosome aberration bioassays. Introduced in 1966, this technique analyzes the number of dicentric chromosomes that occur following an exposure to radiation. An exposure to radiation can cause breakage of the DNA molecule into two nonhomologous chromosomes and produce "sticky ends" that recombine end-to-end. In metaphase, these appear as a single chromosome with two centromeres and are called dicentric. The number of dicentrics in lymphocytes correlates reliably with a given dose of radiation (Table 128–5).

PROGNOSIS

The prognosis of those exposed to radiation varies with the amount of the exposure, the type of medical care received, and the number of casualties in a given exposure scenario. Survival is inversely proportional to the radiation dose absorbed; even the relatively radioresistant cell types can be killed by large amounts of radiation. For these reasons, an acute dose of 20 Gy or more

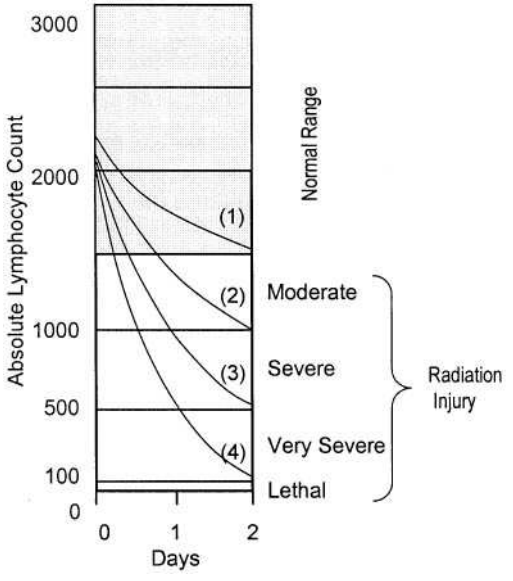


FIG. 128–2. Classic Andrews lymphocyte depletion curves with accompanying clinical severity curves. Curves 1–4 correspond to whole body exposures of 3.1, 4.4, 5.6, and 7.1 Gy, respectively. (From Goans RE, Holloway EC, Berger ME, Ricks RC: Early dose assessment following severe radiation accidents. Health Phys 1997;72:513–518.)

is considered supralethal. Historically, those who were exposed to greater than 10 Gy died despite care. Some authors suggest that those exposed to 10 Gy or greater be given supportive and comfort care only as their survival is considered unlikely.

Within the group exposed to 5–10 Gy, depending on the dose received, there may be milder forms of CNS and cardiovascular syndromes that last for a longer time. A severe GI syndrome in which high fever and persistent hematochezia are present, suggests a poor prognosis. This syndrome may overlap with a severe form of the hematopoietic syndrome in which damage to

TABLE 128–5. Biodosimetry Tools

Dose Estimate (Gy)	Time to Onset of Vomiting (Hours)	Rate Constant for Lymphocyte Depletion	Dicentric Chromosomes in Human Peripheral Blood Lymphocytes (per 1000 Cells)
0	n/a	—	1–2
1	>24	0.126	88
2	4.5	0.252	234
3	2.5	0.378	439
4	1.75	0.5	703
5	1.25	0.63	1024

bone marrow stem cells is so severe that bone marrow function may not recover for weeks or months. These patients are likely to require bone marrow transplantation as well as multiple transfusions of platelets and red blood cells, optimal supportive care, and infection control to survive.

Patients exposed to radiation in the range of 2–5 Gy are likely to survive with medical care. Although the median lethal dose of radiation for humans is estimated to be 4.5 Gy, the manifestations of ARS is similar to those noted above but is likely to be delayed and less severe. Many patients do survive without bone marrow transplantation if supportive care optimizes fluid and electrolyte replacement and controls bleeding and infection. Survival is expected for those patients acutely exposed to less than 2 Gy with little medical intervention necessary.

MANAGEMENT

Initial Assessment

All patients should have stabilization of their airway, breathing, and circulation. Field triage protocols, according to the kind of event, will designate patients as minor, delayed, immediate, or deceased, depending on their burns or physical trauma, and will not be altered because of their radiation exposure. Decontamination should proceed in the field taking care not to contaminate prehospital providers or equipment. Prehospital personnel should use personal protective equipment as well as Geiger counters.

Initial Emergency Department Management

When one or more patients who have been exposed to massive irradiation present to the emergency department, attention must first be paid to the more conventional injuries that may also be present. If a patient should require surgery, the Armed Forces Radiobiology Research Institute (AFRRI) recommends that surgery proceed immediately because of the delayed and impaired wound healing associated with irradiated tissue.

Locally, the radiation safety officer, the medical toxicologist, and the medical oncologist will lend their expertise to the emergency physician to determine the risk of the contaminant, begin appropriate testing to determine the biologic effect, and to initiate medical therapy if warranted. Larger or complex exposures may require the expertise of the Radiation Emergency Assistance Center based in Oak Ridge, Tennessee (865-576-3131, Monday–Friday, 8 A.M.–4:30 P.M. EST; after hours call 865-576-1005), which can provide valuable support.

Decontamination

All clothing should be removed, and patients should be thoroughly washed with soap and water. This can remove up to 95% of radioactive material from the patient. Open wounds should be carefully scrubbed to minimize the risk of internal contamination. A portable dosimeter may assist in external decontamination. If the patient was exposed to neutron radiation such as from a nuclear reactor, blood-sample testing for induced ^{24}Na by γ-spectrophotometric analysis may help as an additional indicator of total dose received. All clothing and liquid used to decontaminate must be collected and be clearly marked as radioactive waste.

Triage

It is critical for patients exposed to a large dose of radiation to be triaged according to the dose so that a management plan can be created for them. There

are many proposed stages of the various subsyndromes of ARS to help with this dosimetry, but in general, we may consider three groups: exposure to less than 2 Gy, 2–4 Gy, and greater than 4 Gy. Those exposed to less than 2 Gy may experience some of the hematopoietic syndrome, but may be followed as an outpatient with or without cytokine therapy. With exposure to 2–4 Gy, the hematopoietic syndrome is likely and may be severe, but at this dose the GI syndrome is unlikely to be a major complication. Hospitalization is recommended, at least initially, for more accurate dosimetry and supportive care, including the early initiation of cytokine therapy. Exposure to greater than 4 Gy means a severe hematopoietic syndrome and, likely, a severe GI syndrome as well. These patients are likely to require an intensive care setting and substantial supportive care for their survival.

Medical Management

As with thermal burns, peripheral intravenous lines are more prone to infection, and central venous access is recommended. Fluid replacement may begin with crystalloid solution where the rate will be modified by recorded inputs and outputs and assessment of surface area burns, if any. Emergency management of emesis and pain may be difficult in those patients who received a high dose of radiation. Many types of antiemetics are used to control an irradiated patient's vomiting. The 5-HT_3 antagonists, ondansetron and granisetron, are particularly effective in this setting. Mild pain may be managed with acetaminophen, but nonsteroidal antiinflammatory medications are not recommended, as they may exacerbate gastrointestinal bleeding in a patient for whom bleeding may soon become difficult to control. Morphine is recommended for the management of more severe pain, which may develop within a few hours after the injury from burns, mucositis, and other complications. As with burn patients, prophylactic use of antibiotics is not recommended.

It is important to obtain a complete blood count (CBC) as soon as possible after exposure to begin biodosimetry estimation, as well as for blood typing. The timing of prodromal signs, such as vomiting, and calculation of the rate constant for lymphocyte depletion help to estimate the dose of radiation to which the patient was exposed. Ideally, a CBC is obtained three times a day for the first 2–3 days following exposure. Some authors recommend initiation of cytokine therapy as soon as possible if the estimated exposure dose is 3 Gy or greater. A threshold of 2 Gy may be used for children younger than 12 years of age and for adults older than 60 years of age as these patients may be relatively more sensitive to the toxic effects of radiation. Blood typing early is important because the patient may require transfusions of red blood cells and platelets. Use of irradiated cells is recommended to avoid graft-versus-host disease. To maximize survival, patients with a severe radiation exposure should be treated as other severely burned or immunocompromised patients regarding their risk of infection.

Special Management Techniques

The colony-stimulating factors, granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, prime neutrophil microbicidal activity and accelerate neutrophil recovery. Spared hematopoietic stem cells in patients with significant whole-body or partial radiation exposures can be stimulated to proliferate in this manner. Although there is no conclusive evidence that early administration is critical for best outcome for these patients, colony-stimulating factor therapy should be initiated as early as possible following the

diagnosis of a 3 Gy or greater exposure. Following Chernobyl, 13 patients received bone marrow transplantation for hematopoietic support until their irradiated bone marrow could recover. Bone marrow transplantation does not change the mortality risk from the other subsyndromes of ARS. Some authors believe there is limited indication for stem cell transplantation when there is also severe radiation injury to organ systems other than the hematopoietic system. Probiotics is the introduction of selective nonpathogenic strains of *Lactobacillus* and *Bifidobacteria* into the gastrointestinal tract to suppress the number of pathogens and should be routinely administered.

Incorporation of radionuclides presents a challenge to the treating physicians where the goal is removal of an internal store of the radioactive material. Both Ca-DTPA and Zn-DTPA were approved in August 2004 by the FDA for human use for decontamination of plutonium, americium, and curium, and both are considered useful in the elimination of soluble uranium salts (nitrates and chlorides not oxides) as well. Prussian blue, ferric hexacyanoferrate, has been used for many years to treat thallium poisoning. Because it absorbs cesium ions, it is used in fission product recovery and is therefore useful in chelation therapy for patients contaminated with cesium (see Antidotes in Brief: Prussian Blue).

^{131}I is one of the key fission products that may be released from a nuclear power facility in an incident such as happened at Chernobyl. The increase of thyroid cancer observed in atomic bomb survivors and in those contaminated from the Chernobyl event prompted the International Atomic Energy Agency (IAEA) to establish intervention criteria for a radiation emergency of an effective dose equivalent of 100 mSv. Supplying stable iodide to the thyroid, which acts as a blocking agent, reduces the uptake of ^{131}I. This treatment, which should begin as soon as the environmental contamination has occurred, will limit the deterministic and stochastic effects of radioactive iodine uptake in thyroid tissue, particularly in children. KI is FDA approved as a nonprescription drug and is available as 130-mg tablets that can be either split or dissolved in liquid for the smaller doses (Table 128–6).

PREGNANCY AND RADIATION

Unfortunately, there is little direct information concerning the effects of radiation in early human pregnancy. Experimental data using rats and mice show

TABLE 128–6. Potassium Iodide Regimen

Age	Dosage
>18–40 years	130 mg
3–18 years	65 mg
1 month–3 years	32 mg
Newborn–1 month	16 mg

For children 18 years and younger, when there is prolonged risk for inhaled radioactive iodine, it is recommended that the indicated dose be repeated daily until the risk is considered past. This recommendation also applies to lactating mothers.

For adults younger than 40 years, repeated dosing is not indicated in favor of controlling food intake, eg, abstention from drinking milk during the time of contamination.

For adults older than 40 years, the risk of radiation-induced cancer is so low that iodide prophylaxis is not indicated, unless the radiation amount is on the order of 5 Gy, but this is unlikely.

increased mortality rates both in vitro and in vivo following irradiation, as well as a dose–response curve that depicts incremental increases in radiation dose corresponding to increasingly greater effects in causing malformations. The most important sources of information concerning the teratogenic effects of fetal irradiation are the survivors of the nuclear bomb blasts of World War II. The three principal risks to a fetus following radiation exposure are congenital abnormalities, severe mental retardation, and the late development of a neoplasm. The embryo is at particular risk because of its rapid development, and there are several periods of particular sensitivity, so that irradiation at specific times is associated with increased risk of specific problems. Roughly speaking, uterine absorption of 0.1–0.15 Sv during the first 2 weeks after conception risks fetal lethality. During weeks 3–7 postconception, uterine doses of 0.05–0.5 Sv risks congenital abnormalities, growth retardation, and small head size that may be accompanied by mental retardation. During weeks 8–25 postconception, the risk is severe mental retardation, which begins to decrease at the 16th week. Consideration should always be given to the potential maternal benefit of the radiologic procedure as well as the potential risk to the fetus. However, the vast majority of routine diagnostic imaging procedures impart less than 0.05 Sv to the fetus and so are considered a negligible risk.

PEDIATRICS AND RADIATION

The use of CT scanning in children has markedly increased over the last 20 years. One hospital's survey showed a 92% increase in abdominal and pelvic CT examinations from 1996–1999 for children younger than 15 years old. Although it is difficult to estimate the increased incidence of cancer rates caused by LET radiation, there are reports that attribute a greater lifetime risk for cancer mortality resulting from CT examination in children. This risk is compounded by the tendency not to adjust the radiation dose given to a child during a CT examination from the amount given to adults. Together, these trends may mean increased radiation-induced mortality over the lifetime of the patient resulting from medical evaluation.

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Section II. Poison Centers and Epidemiology

129 Poison Prevention and Education

Preventing poisonings and improving access to poison center services are both national public health issues. Two objectives in the Injury and Violence Prevention section of *Healthy People 2010* relate to poison prevention. Objective 15-7 is to *reduce nonfatal poisonings* and Objective 15-8 is to *reduce deaths caused by poisoning*. Objective 1-12 in Access to Quality Health Services focuses on national access to poison centers and recommends *establishing a single toll-free telephone number for access to poison control centers on a 24-hour basis throughout the United States.* This objective was achieved in 2002. Community-based public education programs at poison centers are designed to help meet these public health objectives.

LEGISLATION AND POISON PREVENTION

National Poison Prevention Week

In 1961, Public Law 87-319, designated National Poison Prevention Week (PPW) to raise awareness of the dangers of unintentional poisonings. During PPW, poison centers and other organizations around the country organize events and activities to promote poison prevention.

Child-Resistant Packaging Act

In 1970, the Poison Prevention Packaging Act was passed. This law requires that the Consumer Product Safety Commission (CPSC) mandate the use of child-resistant containers for toxic household substances. In 1974, oral prescription medications were included in this requirement.

Toll-Free Access to Poison Centers

In 2000, the Poison Control Center Enhancement and Awareness Act was enacted with a goal of nationwide access to poison centers. A toll-free number (1-800-222-1222) has established access for all US poison centers.

THE ROLE OF PUBLIC EDUCATORS IN POISON CENTERS

Nationally, poison centers employ 100 public educators who encompass a range of educational backgrounds, including nurses, pharmacists, health educators, and teachers. The primary goals of public education programs at poison centers are to teach poison prevention techniques (primary prevention) and to raise awareness about available services should a poisoning occur (secondary prevention).

NEEDS ASSESSMENTS

To develop successful poison education programs, educators must analyze demographic data, call volume rates, cultural issues, language, and barriers to calling a poison center.

Geographic Information Systems (GIS) software offers a way for poison centers to visually map demographic data. Using GIS for population-based programs is recommended for developing social marketing campaigns, health education programs, outreach efforts, and coalition building. Focus groups provide another useful qualitative method for poison center educators to identify perceptions about calling the poison center.

POISON EDUCATION PROGRAMS

Of the 2 million annual calls to poison centers nationally, more than 1 million involve children younger than the 5 years old. As a result, programs to teach caregivers about primary and secondary prevention techniques have been the focus of education efforts. Typically, these programs focus on teaching poison prevention tips (Table 129–1) and raising awareness of poison center services. Historically, seniors have not been a priority population for poison center education resources, but this emphasis is shifting.

Interventions Targeting Health Behavior

Unintentional poisonings frequently happen when children are left unattended for a brief period of time (<5 minutes) and a toxic product in use or recently purchased is left within reach of the unattended child. Interventions may be conducted with caregivers after a potential poisoning exposure occurs. An injury-prevention program provided to caregivers of young children after a home injury is effective, particularly regarding poison prevention information and the use of safety devices.

The population at highest risk for poisoning fatalities is older adults. Recommendations have been made to educate older adults about potential problems with medication use, storage of products, and the services of the poison center.

Community-Wide Interventions

A recent review of pediatric literature focusing on community-based poisoning prevention programs found only four studies using poisoning rates as the outcome measure. There is a need for more studies to measure community-based poison-prevention efforts. Mass-mailing campaigns have been evaluated as a relatively inexpensive way to raise awareness and increase poison center call volume. In most instances, this technique has been ineffective.

Multilingual Populations

Language and culture must be addressed when planning community-based programs. A number of studies demonstrate that caregivers are less likely to call

TABLE 129–1. Poison Prevention Tips

- Identify poisons inside and outside the home
- Keep poisons out of reach in a locked cabinet
- Keep products in their original containers
- Never keep food and nonfood items together
- Install carbon monoxide detectors in sleeping areas
- Keep plants out of reach of children and pets
- Use child-resistant containers
- Post the poison center number on all telephones

the poison center when English is not their primary language because of concerns including confidentiality and language barriers. It is important to consider employment of bilingual staff as public educators when trying to expand public awareness. Health education programs, including mass media campaigns, that are designed to accurately reflect the cultural identity—language, beliefs, roles—of the targeted population are more likely to be accepted.

Literacy/Health Literacy

Literacy is another area of consideration when designing poison education programs. Health literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions." This encompasses the ability to read, understand, and discuss medical information. It is estimated that approximately 90 million Americans—half the adult population—have limited literacy skills and are often unable to understand health information and complete the tasks required by the healthcare system.

Applying Health Education Principles to Poison Education Programs

Health education involves planning, implementing and evaluating programs based on theories and models. Both the Health Belief Model (HBM) and social cognitive theory (SCT) incorporate the concept of self-efficacy and are applicable when designing poison-prevention interventions and mass-media campaigns. Self-efficacy is the individual's belief that he or she will be able to accomplish the task requested. It is often believed that self-efficacy is necessary for changing health behaviors. The SCT suggests that individuals must have the confidence that they can successfully make the behavior change and that the benefits outweigh the costs. The HBM suggests that individuals are more likely to make health behavior changes based on perceived risk susceptibility, severity, potential barriers, and self-efficacy. Again, decisions are made when actions are seen as potentially more beneficial to the individual than the perceived risks associated with surmounting the current barriers.

130 Poison Information Centers and Poison Epidemiology

HISTORY

In 1950, the American Academy of Pediatrics created a Committee on Accident Prevention to explore methods to reduce injuries in young children. A survey by that committee demonstrated that injuries resulting from unintentional poisoning were a significant cause of childhood morbidity. Simultaneously came the realizations that a source of reliable information on the active ingredients of common household products was lacking and that there were few accepted methods for treating poisoned patients. In response to this void, the first poison center was created in Chicago in 1953. The poison center of today is charged with many of the same mandates as the original centers, including maintaining a database; providing information to public and health professionals, collecting epidemiologic data on the incidence and severity of poisoning; preventing unnecessary hospitalizations following exposure; and educating healthcare professionals on the diagnosis and treatment of poisoning. However, a crucial test of the usefulness of poison centers will be their ability to demonstrate a reduction in poison-related mortality.

MAINTAINING A DATABASE ON PRODUCT CONTENTS AND POISON MANAGEMENT

With the evolution of information technology, poison centers are no longer perceived as the sole guardians of toxicology information. Although these services are still essential for the public at large, and those professionals away from their computers, a predictable decline in poison center use has paralleled growth in information availability. A study demonstrated that 82.6% of emergency physicians who had POISINDEX available in their institutions did not routinely consult the poison center. An initial analysis might suggest that this is an acceptable trend in that it both allows physicians to respond more rapidly to patient needs and poison information centers to be more available to those individuals who do not have access to this information system. However, this practice of "not calling" undermines the efforts of poison information centers to gather epidemiologic data. Also, because most databases are designed to provide information about known entities, they perform poorly when dealing with unknown and unclear scenarios. Thus, although originally designed as providers of information, poison centers must now be considered valued consultants, with staff who not only provide content information but also interpret clinical material and link both to appropriate management strategies. An illustrative example of the value of poison centers can be drawn from the use of flumazenil for benzodiazepine overdose. Although it may easily be determined by anyone capable of using an index that flumazenil is an antidote for benzodiazepine overdoses, many subtle characteristics of the patient or the overdose often contraindicate its use. A prospective study determined that when flumazenil was used before consultation with the poison information center, contraindications were present in 10 (71%) of 14 cases, resulting in one serious adverse event.

COLLECTING POISON EPIDEMIOLOGY DATA

Recent data demonstrate that poisoning is the third leading cause of injury-related fatalities, ranking behind motor vehicle crash and firearm use. Understanding the evolving trends in poisoning is essential to the development of enhanced surveillance, prevention, and education programs designed to reduce unintentional poisoning. Although data can be analyzed from numerous sources, such as death certificates, hospital discharge coding records, and poison information centers, it is essential to recognize the biases that are inherent in each of these reports. Because not all significant poisoning results in either hospitalization or fatality, data from poison centers appear to offer a unique perspective.

Unfortunately, the data collected and disseminated by poison centers is defined by the term "exposures." Many exposures are of no clinical consequence because of the properties of the xenobiotic involved, the magnitude or duration of the exposure, or uncertainty as to whether an actual exposure has occurred; therefore, data collected by poison information centers represent a limited and ill-defined measure of poisoning. The situation is further confounded by multiple biases that are introduced by the actual reporting process, which first and foremost is voluntary and passive. Because the majority of calls concern self-reported data that come from the home and are never subsequently confirmed, a significant percentage of existing data may actually represent potential or possible exposures, with the potential for resultant large statistical errors introduced into the database. Reporting biases serve as another clear example of problems with poison center data.

Fatal Poisoning

A 4-year study compared deaths from poisoning reported to the Rhode Island medical examiner with those reported to the area poison center. Not surprisingly, the medical examiner reported many more deaths: 369 compared to 45 reported by the poison center. Although the majority of the cases not reported to the poison center were victims who died at home, were pronounced dead on arrival to the hospital, or those in whom poisoning was not suspected until the postmortem analysis, 79 patients who subsequently became unreported fatalities were actually admitted to the hospital with a suspected poisoning. In ten of these cases, the authors concluded that a toxicology consultation might have altered the outcome. Similar studies confirm these findings.

Nonfatal Poisoning

A 1-year retrospective review demonstrated that only 26% (123/470) of poisoned patients who were treated in a particular emergency department were reported to the poison center. Interestingly, only 3% of inhalational exposures were reported, compared with 95% of cyclic antidepressant ingestions. Similarly, in a survey, physicians reported that they would "almost never" contact the poison center for asymptomatic exposures (62.9%), chronic toxicity (50.4%), or simply to assist in establishing a reliable database (90.2%).

Occupational Exposures

A number of federal and state government-funded agencies, such as National Institute for Occupational Safety and Health (NIOSH), Occupational Safety

and Health Administration (OSHA), and Agency for Toxic Substances and Disease Registry (ATSDR), exist to prevent occupational illness, to educate the public, and to collect data on exposures to occupational toxins. Discrepancies exist between poison information data and the data collected by governmental agencies. A 6-month survey in California noted that only 15.9% of the occupational cases reported to the poison center were captured by a state reporting system.

Adverse Drug Events and Medication Errors

The ease of 24-hour telephone access, combined with the ability to consult with a health professional, make poison centers ideal resources for reporting of adverse drug events (ADEs). Yet, more than 76% of physicians surveyed stated that they would "almost never" contact the poison center regarding adverse drug reactions. Moreover, in one study, 53.6% of poison centers stated that they had not submitted any of their ADE data to the Food and Drug Administration's MedWatch program.

Drugs of Abuse

Poison centers also collect data on exposures to drugs of abuse and misuse. Because most substance abuse does not result in immediate interactions with the healthcare system, other databases such as the National Institute on Drug Abuse (NIDA) Household Survey (now referred to as the Monitoring the Future Study) might better reflect substance abuse trends.

Grossly Underreported Xenobiotics

There is little doubt that alcohol and tobacco are the most common xenobiotics intentionally used and misused in our society. Although their toxicologic manifestations can be acute and severe, chronic subclinical poisoning often goes unnoticed for many years. Similarly, more than 1 million American children have lead concentrations above 10 μg/dL and elevated concentrations of polychlorinated biphenyls (PCBs) can be found in countless adults and children. We must remain cognizant of these facts when we read that plants, cleaning products, and cosmetics are the most common exposures to xenobiotics. These are only the most common "reported" exposures.

Using the Existing Data

With the current limitations of the Toxic Exposure Surveillance System (TESS) data, it should be clear that neither the numerator nor the denominator of poisoning can be easily appreciated. Analysis of these data for trends may be more useful because the inherent biases involved in TESS reporting are probably consistent over many years. Despite its limitations, TESS data have significant usefulness. It is often an *exposure* rather than an actual *poisoning* that provides the impetus for contact with healthcare. For those exposures that are unlikely to be clinically consequential, the poison center can intervene to prevent potentially harmful attempts at home decontamination and costly unnecessary visits to healthcare providers. Interactions with parents at a time of perceived crisis also provides a "teachable moment" that may help prevent a more consequential exposure in the future.

PREVENTING UNNECESSARY HOSPITALIZATIONS FOLLOWING EXPOSURE

When visits to pediatric emergency departments for acute poisoning were analyzed, one study demonstrated that 95% of parents had not contacted the poison center before coming to the hospital. Sixty-four percent of those children required no hospital services. In contrast, when parents called the poison center first, fewer than 1% sought emergency services. When 589 callers to one poison center were surveyed, 464 (79%) stated that they would have used the emergency care system if the poison center was unavailable. Suggesting simple techniques or reassurance can successfully reduce hospital visits. The national average cost to the poison center for a single human exposure call is less than $35. A federally funded study concluded that in 1 year, poison centers reduced the number of patients who were treated and not hospitalized by 350,000 and reduced hospitalizations by an additional 40,000 patients. Each call to a poison center prevented at least $175 in subsequent medical costs, providing strong theoretical evidence to support the cost efficacy of poison centers.

PROVIDING EDUCATION FOR THE PUBLIC AND HEALTH PROFESSIONALS

Poison center staff work closely with physicians, community health educators, community support groups, and parent–teacher associations to develop poison-prevention activities. Table 130–1 lists common strategies advocated to prevent poisoning.

DEVELOPMENT OF PUBLIC HEALTH INITIATIVES

The initial public health efforts of poison centers focused on attempts to alter product concentration and to enhance product labeling and packaging. Current events have also increased poison center activities in preparedness for di-

TABLE 130–1. Common Strategies Advocated to Help Prevent Poisoning

- All xenobiotics should be kept in their original containers. Food and drink containers should never be used for the excess of a xenobiotic.
- Never store xenobiotics in unlocked cabinets under the sink.
- Apply locks to medicine cabinets that are within the reach of a child.
- In the absence of a lock, the more toxic xenobiotics should be stored on the highest shelves.
- Xenobiotics should never be left in the glove compartment of the family car.
- Parents should buy or accept medication only if it is in a child-resistant container.
- Medication should be considered as medicine, not a plaything and certainly not candy.
- Adults should not take their medications in front of children: This will limit exposure to drug-taking role models that may become objects of imitative behavior.
- Unused portions of prescription medications should be discarded by flushing the excess down the toilet at the completion of drug therapy.
- Activated charcoal should be readily available in the home for use if directed by a poison information specialist or clinician.
- Since it should be anticipated that about 10% of children who have ingested a poison will do so again within a year, these children should receive an enhanced level of supervision.

sasters resulting from radiologic, biologic, and chemical terrorism. Additional collaboration with governmental agencies such as the Centers for Disease Control and Prevention (CDC) and ATSDR continually expand the role of medical toxicology in community health.

131 International Perspectives in Medical Toxicology

Poisoning is a worldwide problem. Not only are there significant variations in patterns of poisoning between countries, but variations in poisoning patterns within any given country may be significant, especially when comparing wealthier urban centers with agrarian, often poorer, rural areas. Although the majority of healthcare and academic resources are concentrated in urban centers, it is in the countryside where much of the mortality from acute poisoning occurs. The accessibility of pesticides to rural people and their lethality has a profound influence on global poisoning patterns. Public health education about poisons and laws limiting access to the most highly toxic chemicals are practically absent in much of the world. Life-saving, yet basic, resources, such as mechanical ventilation, antidotes, and antivenoms, are in particularly short supply.

The challenges of treating acute poisoning are complex and require a coordinated effort between governments, academic centers, and individual toxicologists. In countries where one of these elements is not functional, efforts should be directed toward supporting the existing infrastructure pending the development of other key resources.

THE GLOBAL HEALTH BURDEN OF POISONINGS

In 1990, the results of several small studies were extrapolated to suggest that there were 2 million episodes of deliberate self-poisoning with pesticides annually in the Asia-Pacific region alone, and that the mortality rate was 10%, thus producing 200,000 deaths annually. In the industrialized world, reported mortality rates from intentional ingestions range from 0.5–1.0%. Occupational or unintentional exposure to pesticides in the same region was estimated to effect 1 million people acutely, and as many as 25 million subacutely. Only 20,000 annual deaths, however, were attributed to unintentional pesticide exposure (mortality rate: 0.8–2.0%). In 2000, World Health Organization (WHO) statistics placed poisoning within the top 15 causes of death worldwide for persons ages 5–44 years old. Unfortunately, injury surveillance systems are in their infancy in most parts of the world. It is estimated that 99% of poisoning fatalities worldwide occur in the developing world. The single most important factor contributing to the high case fatality rate associated with self-poisoning in the developing world is the ease of availability of highly toxic substances in the home. Inadequate pesticide storage practices, unclear labeling and the intrinsic lethality of these compounds are also contributory factors.

Deliberate self-poisoning with organic phosphorus (OP) pesticides puts a high cost on the healthcare system. In one study examining the experience in Sri Lanka, OP pesticide poisoning was responsible for 943 (36%) of 2559 hospital admissions for poisoning. The mortality rate for OP poisoning was 21%, and pesticide-poisoned patients occupied 41% of all medical intensive care beds. In contrast, a 40-year retrospective study of poisoning in England and Wales found that OP pesticides were responsible for only 68 (0.0007%) of 87,385 deaths. The dramatic differences between mortality rates documented in the industrialized world, where pesticide exposures are relatively rare events and primarily unintentional, and the developing world, where massive intentional ingestion is commonplace, highlight the profound differences in terms of epidemiology and resources between these environments.

Snakebites and envenomations by other animals represent a significant cause of morbidity and mortality in the developing world. Venomous snakes are found on all continents, with the exception of Antarctica, although the majority of species are found in equatorial, tropical, or subtropical environments. The World Health Organization estimates that there are 5 million snakebites each year, about half of which result in potential envenomation. While some disagreement among experts exists, poisonous snakebites are responsible for at least 125,000 deaths annually. In contrast, fewer than 100 fatal snakebites per year are estimated to occur in Europe, the United States, Canada, and Australia combined. The mainstay of effective therapy for severe snakebite is antivenom. However, many of the currently available antivenoms are either prohibitively expensive, ineffective, or have a high rate of adverse reactions. Equally important, many antivenoms must be refrigerated, making them impractical therapies in many areas of the developing world.

Poisoning with pharmaceutical products is reported throughout the world. In general, the use of pharmaceuticals is more common in urban areas where access is easier and there are more people with the means to buy medications. The pharmacopeia available in the developing world is smaller than in the industrialized world, with the exception of drugs to treat tropical diseases that may be indigenous to a particular area.

The use of traditional medicines is common in the developing world. Also because traditional medicines are frequently used by immigrants from the developing world, it is reasonable to assume that immigrants have full access to the traditional pharmacopeia of their country of origin. Intoxication with traditional Chinese medicines is increasingly reported. A review of traditional Chinese medicines found 2788 reports of adverse drug reactions, representing 40% of all products (herbs and pharmaceuticals). The most commonly reported products were aconite root, followed by *Triperygium wilfordihoof*, and *Isatis tinctoria L.* Adulterants are also common in traditional Chinese medicines, particularly synthetic pharmaceuticals and heavy metals. A Taiwanese study of 2609 samples found that 23% were adulterated with pharmaceutical products (primarily caffeine, nonsteroidal antiinflammatory drugs, acetaminophen, and diuretics).

Multiple other examples highlight differences between developing and developed nations.

REDUCING POISONING MORTALITY GLOBALLY

Recognition of the fact that self-poisoning with pesticides is responsible for the majority of poisoning deaths worldwide compels action to reduce the mortality associated with these agents. Strategies to reduce the health effects of pesticides should take into account concerns regarding both environmental and human toxicity, and anticipate which xenobiotics will replace the most highly toxic chemicals as they are phased out of use.

Four basic strategies have been proposed to limit the health impact of the most hazardous chemicals worldwide (Table 131–1). Voluntary interventions include international policy statements and industrial pesticide initiatives. In 1985, the Food and Agriculture Organization (FAO) of the United Nations issued a strongly worded document, the *Code of Conduct on the Distribution and Use of Pesticides*. The pesticide industry has also worked in cooperation with the FAO to remove or destroy large stockpiles of obsolete or banned pesticides in the developing world. CropLife International is an industry-sponsored initia-

TABLE 131–1. Strategies to Reduce Pesticide Availability in the Developing World

1. Voluntary guidelines, safe use initiatives, and international policy instruments
2. Changing farming practices: integrated pest management (IPM) and plant biotechnology
3. Direct restriction of pesticide use
4. A minimum pesticide list

Adapted from Konradsen F, van der Hoek W, Cole DC, et al: Reducing acute poisoning in developing countries—options for restricting the availability of pesticides. Toxicology 2003;192:249–261.

tive that claims to reduce the health burden of pesticide poisoning through safe use and Integrated Pest Management (IPM) programs (www.croplife.org/default/aspx). The cost-effectiveness of industry sponsored Safe Use of Pesticides programs, however, is questionable. Voluntary initiatives, unfortunately, suffer from a lack of resources, a shortage of political will, and nonexistent enforcement mechanisms.

Restricting access to pesticides is the key step in reducing the number of cases and the mortality of intentional ingestions. National programs that remove specifically harmful pesticides demonstrate an effect on mortality. In Samoa, for example, completed suicide rates climbed after the introduction of paraquat; when paraquat became less available because of financial constraints, combined with a public education campaign, poisoning case fatality rates returned to previous levels. Similarly, when parathion was recognized to be responsible for more than 90% of pesticide deaths in Jordan, it was banned, resulting in a dramatic reduction in poisoning deaths.

INTERNATIONAL RESOURCES

Through the collaboration of the Society of Toxicology (USA) and the European Society of Toxicology, the International Union of Toxicology (IUTOX) was established in 1980 with the goal of fostering international cooperation in the field of toxicology. The IUTOX, which was initially formed by eight national toxicology organizations, now includes more than 40 member societies from around the world. The IUTOX is a membership organization of toxicology professionals and functions to facilitate cooperation between toxicology societies.

TABLE 131–2. Examples of Open Access Web Sites That Provide Toxicology Information

1. The International Programme for Chemical Safety (WHO) http://www.who.int/ipcs/en/
2. International Union of Toxicology http://www.iutox.org/index.asp
3. The American Academy of Clinical Toxicology http://www.clintox.org/
4. TOXNET, National Library of Medicine (USA) http://toxnet.nlm.nih.gov/
5. The Canadian Network of Toxicology Centres (Canada) http://www.uoguelph.ca/cntc/
6. VIASALUS Toxicology, in Spanish and Catalan (Spain) http://www.viasalus.com/vs/B2P/cn/toxi/index.jsp
7. Centers for Disease Control (USA) http://www.cdc.gov/
8. YellowTox (WHO), a global directory of toxicologists http://www.who.int/ipcs/poisons/centre/directory/en/

The International Programme for Chemical Safety (IPCS) provides extensive information via the World Wide Web and numerous publications. The IPCS is supported by the World Health Organization, the International Labor Organisation, and the United Nations Environment Programme, with many national organizations contributing useful information and resources. The Poisons Information Monographs provide extensive peer-reviewed information on chemicals, pharmaceuticals, poisonous plants, and poisonous and venomous animals. Although this information is not specifically evidence based, this internationally reviewed document represents consensus opinion from poison control centers around the world. The IPCS materials are available in French, English, Spanish, and Portuguese.

Table 131–2 lists public access websites that provide toxicology information.

132 Principles of Epidemiology and Research Design

Advances in clinical medicine are usually achieved through a typical scientific method. First, astute clinicians make interesting observations. These observations lead to the generation of hypotheses. Research questions are analyzed with an epidemiologic investigation, and initial studies are examined with methodologic scrutiny. Initial analytic techniques are improved, and confirmatory studies are performed. Ultimately, models relating cause to effect are formulated.

The field of medical toxicology is rapidly transitioning from a descriptive discipline to one of rigorous scientific exploration. New associations between toxic xenobiotics and diseases are being explored every year. An understanding of basic principles of research design and epidemiology is required to interpret published studies and to lay the groundwork for future investigation in toxicology.

EPIDEMIOLOGIC TECHNIQUES AVAILABLE TO INVESTIGATE CLINICAL PROBLEMS

Table 132–1 lists the different study formats.

Study Designs

Descriptive case reporting serves a valuable purpose in describing the characteristics of a medical condition or procedure and remains a fundamental tool of epidemiologic investigation. A *case report* is a clinical description of a single patient or procedure with respect to a situation. Case reports are most useful for hypothesis generation. However, single case reports are not generalizable, as the reported situation may be atypical. A number of case reports can be grouped, on the basis of similarities, into a *case series.* Case series can be used to characterize an illness or syndrome, but without a control group they are severely limited in proving cause and effect. *Cross-sectional studies* assess a population for the presence or absence of an exposure and condition simultaneously. Such data often provide estimates of *prevalence*—the fraction of individuals in a population sharing a characteristic or condition at a point in time. These studies, particularly helpful in public health planning, are extremely useful in monitoring common environmental exposures, such as childhood lead poisoning, or population-wide drug use, such as occurs with tobacco, marijuana, and alcohol. An *analysis of secular trends* is a study type that compares changes in illness over time or geography to changes in risk factors. These analyses often lend circumstantial support to a hypothesis; however, because of the ecologic nature of their design, individual data on risk factors are not available to allow exclusion of alternative hypotheses that are also consistent with the data. *Case-control studies* compare affected, treated, or diseased patients (cases) to nonaffected patients (controls) and look for a difference in prior risk factors or exposures. Because subjects are recruited into the study based on prior presence or absence of a particular outcome, case-control studies are always retrospective in nature. They are especially useful when the outcome being studied is rare, and they enable the investigation of any number of potential etiologies for a single disease. *Cohort studies* compare patients with certain risk factors or exposures to those patients without the exposure, then follow these cohorts to see

TABLE 132–1. Types of Epidemiologic Study Designs[a]

Experimental
Clinical trial
Observational: Analytic
Cohort
Case-control
Observational: Descriptive
Analysis of secular trends
Cross-sectional
Case series
Case report

[a]Study designs are listed in descending order from the design that offers the best epidemiologic evidence for association to that which offers the least.

which subjects develop the outcome of interest. In this respect, they allow the comparison of *incidence* (the number of new outcomes occurring within a population initially free of disease over a period of time) between populations that share an exposure and populations that do not. They are particularly well suited to investigations in which the outcome of interest is relatively common.

Experimental studies are those in which the treatment, risk factor, or exposure of interest can be controlled by the investigator to study differences in outcome between the groups. The prototype is the randomized, blinded, controlled clinical trial. Among epidemiologic study types, these provide the most convincing demonstration of causality. Unfortunately, interventional studies are the most complex to perform, and several questions must be addressed by investigators before performing a clinical trial. Human clinical trials have been especially difficult to apply to the practice of toxicology. Table 132–2 lists the characteristics of poisoned patients that hamper attempts at clinical trials.

MEASURES USED TO QUANTIFY THE STRENGTH OF AN EPIDEMIOLOGIC ASSOCIATION

The *relative risk* can be defined as the incidence of outcome in exposed individuals compared to the incidence of outcome in unexposed individuals, and can be calculated directly from cohort or interventional studies. However, in a case-control study, an investigator chooses the numbers of cases and controls to be studied, so true incidence data are not obtained. In case-control studies an *odds ratio* can be calculated, and the odds ratio will provide an estimate for relative risk in situations where the outcome is rare, such as when the out-

TABLE 132–2. Difficulties in Applying Clinical Trials to Human Poisoning

- It is unethical to intentionally "poison" subjects.
- Poisoned patients represent a broad spectrum of demographic patterns.
- A wide variety of poisons exist.
- Exposures to any single poison are usually limited.
- A limited number of poisoned patients are available at any one study site.
- Uncertainty often exists as to type, quantity, and timing of most poison exposures.
- Poisoning typically results in a relatively short course of illness.

come occurs in fewer than 10% of exposed individuals. A relative risk of 1.0 signifies that an outcome is equally likely to occur whether an individual is exposed or not and implies that no association exists between the exposure and the outcome. A relative risk approaching 0 suggests that an exposure is a marker of protection with regard to the outcome, and a relative risk approaching infinity suggests the exposure predicts a tendency toward the outcome.

MEASURES USED TO QUANTIFY THE SIGNIFICANCE OF AN EPIDEMIOLOGIC ASSOCIATION

The goal of statistical analysis is to determine the degree to which chance can be excluded as the true reason the results of the study were obtained. By convention, statistical analysis typically tests the *null hypothesis*—the hypothesis that there is no association between exposure and outcome. Because analytic studies involve only a sample of the total population, they contain 2 types of inherent error. *Type I error,* also referred to as alpha (α) error, is the likelihood that an investigator may conclude that an association exists when none truly does. *Type II error,* or beta (β) error, is the possibility that an investigator will be unable to find an association when one is really present.

DIFFERENTIATION BETWEEN CLINICAL SIGNIFICANCE AND STATISTICAL SIGNIFICANCE

The finding of a low *p* value indicates a statistically high level of confidence that a difference between study groups exists, but offers no indication that the difference is clinically important. Small actual differences between two groups can become statistically significant if large numbers of subjects are studied. Likewise, impressive associations of cause and effect can seem trivial if few subjects are in a study. The clinical significance of an association is left to the judgment of the individual interpreting a study. Ideally, a working definition of clinical significance is developed before a study is performed.

METHODOLOGIC PROBLEMS FOUND WITHIN CLINICAL STUDIES

Clinical research involving patients is particularly susceptible to *bias*, which can be defined as systematic error in the collection or interpretation of data. Because such error can lead to an inappropriate estimate of the association between an exposure and an outcome, careful evaluation of potential biases affecting a clinical study is of paramount importance. *Selection bias* refers to error introduced into a study by the manner in which subjects are selected for inclusion in the study. *Information bias* refers to error introduced into a study as a result of systematic differences in the quality of data obtained between exposed and unexposed groups, or between those with and without the outcome of interest. The potential for *recall bias* is frequently cited as criticism of retrospective case-control studies. Simply, exposed subjects may have a different capacity to remember than the unexposed. Similarly, *interviewer bias* may occur if study personnel differ in how they solicit, record, or interpret information as a result of knowledge of the subjects' status with regard to exposures or outcomes. *Misclassification bias* occurs when investigators incorrectly categorize subjects with respect to exposure or outcome. Bias is best minimized through careful study design.

Unlike selection and information biases, which are errors introduced into studies primarily by the investigators or subjects, confounding is a special type of problem that may occur within a study as a result of interrelationships

between the exposure of interest and another exposure. *Confounding* is a bias wherein an observed association is not a product of cause and effect but instead results from linking of the exposure of interest to another associated exposure. For example, studies pertaining to adverse effects of drugs of abuse are especially prone to confounding by variables such as concomitant caffeine use, alcohol use, tobacco use, nutritional deficiency, and/or psychiatric illness. Randomization is an important method to assure that unsuspected confounding factors are equally distributed between treatment groups within interventional studies.

EVIDENTIARY CRITERIA USED TO LINK CAUSE AND EFFECT

Association of an exposure to an illness does not necessarily equate to cause and effect. In assessing causation, it must be determined if bias is present in the selection or measurement of exposure or outcome. Table 132–3 provides a list of evidentiary criteria that are often used to support causation. Because in medical toxicology it is virtually impossible to prove causal relationships beyond any doubt, the goal is to build empiric evidence so that associations can be confirmed or refuted with conviction.

EVALUATION OF DIAGNOSTIC TESTS AND CRITERIA

In clinical practice it is often useful to have a test, which may be a laboratory result or clinical paradigm, to help arrive at a diagnosis or predict an outcome. The usefulness of diagnostic testing is often described in terms of sensitivity, specificity, predictive value of a positive test (PPV), and predictive value of a negative test (NPV). A cross-sectional design is often used to study diagnostic tests, as we seek to determine the prevalence of positive tests among the diseased (*sensitivity*), and the prevalence of negative tests among the healthy (*specificity*). A perfect test would be highly sensitive and specific, but this is seldom possible in medical toxicology. A highly sensitive test is often used in screening programs because they rarely lead to false-negative diagnoses. Specific tests are typically used to confirm a diagnosis, as they rarely yield false-positive results. Whereas sensitivity and specificity are inherent properties of a diagnostic test applied to a given population; the probability of disease, based on the results of a test, is highly dependent on the prevalence of disease within the population being tested. The PPV is the probability of having disease in a patient with a positive test; the NPV is the probability of not having disease when the test result is negative. Figure 132–1 illustrates the calculation of the

TABLE 132–3. Criteria Supporting Causation

Study design	Was the association demonstrated in a well-designed study?
Temporality	Does the cause precede the effect?
Strength	What degree of relative risk was demonstrated in the analysis?
Dose response	Does an increased presence of risk factor correlate to greater or more frequent effect?
Consistency	Does the cause and effect hold true in different studies, locations, and populations?
Plausibility	Is the association in accordance with current scientific knowledge?
Specificity	Does the effect occur without the cause in question, or vice versa?

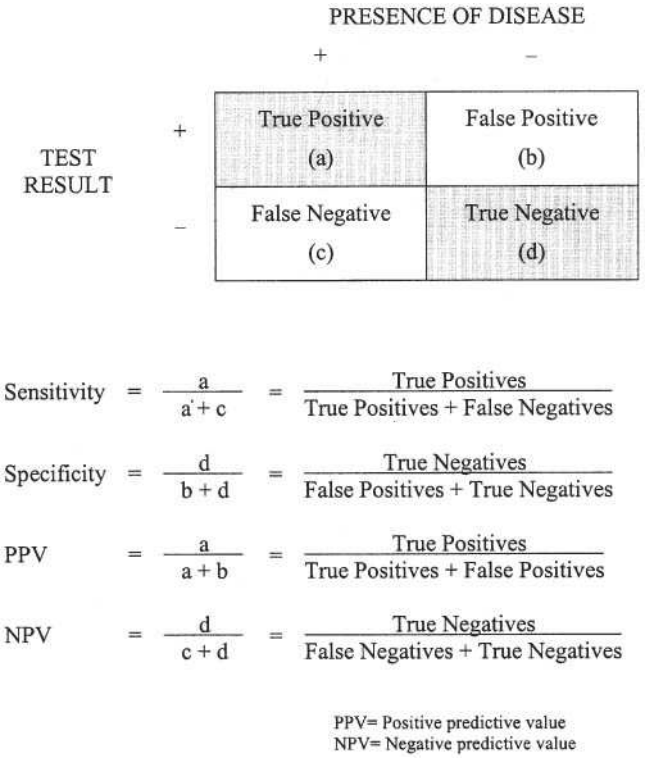


FIG. 132–1. Possible results of diagnostic testing and the statistical characteristics used to describe the usefulness of diagnostic tests. The letters a, b, c, and d represent the numbers of tested individuals with or without the disease of interest.

sensitivity, specificity, PPV, and NPV. It is important to remember that these calculations, too, are subject to bias and that these calculations are best presented with confidence intervals.

133 Adverse Drug Events and Postmarketing Surveillance

Adverse drug events (ADEs) are defined as an untoward effect or outcome associated with use of a drug. In this chapter, the word "drug" will be used for a pharmaceutical product and includes prescription and nonprescription products, as well as dietary supplements. In the United States, all prescription and nonprescription products must be approved by the Food and Drug Administration (FDA) prior to marketing and sale. For complex reasons, dietary supplements fall outside of this legal requirement (Chap. 43).

HISTORY OF THE UNITED STATES DRUG-APPROVAL PROCESS

Today in the United States, approvals of new therapeutic agents are occurring at an unprecedented rate. Before 1900, there was no legal requirement for a company to test a product for safety or efficacy, or even to make valid claims on the drug label. Products such as aspirin-containing heroin were sold as cough syrup. Furthermore, there was no legal requirement for systematic testing of products to determine content or the presence of possible adulterants in product formulations. The Pure Food and Drug Act of 1906 required pharmaceutical manufacturers to meet a standard for the concentration and purity of the drugs they marketed. The Food, Drug and Cosmetic Act of 1938 resulted from a tragedy in which more than 100 patients (mostly children) died from poisoning by an excipient of an oral solution of sulfanilamide. The Food Drug and Cosmetic Act of 1938:

- Required companies to list the ingredients of the product on the product label.
- Required companies to provide the known risks concerning use of the product to physicians or pharmacists.
- Made illegal the misbranding of food or medical products.
- Required companies to test their products for safety before being sold.

Drugs already marketed before 1938 were exempt from the requirement. Also as a direct result of the near release of thalidomide in this country, congressional hearings resulted in the Kefauver-Harris Act of 1968, which required a drug manufacturer or sponsor to:

- File an investigational new drug (IND) application before beginning a clinical study with a drug in humans.
- Demonstrate that the drug was effective for the condition that it was being marketed to treat.
- Provide adequate directions for safe usage of the drug.

Moreover, the act did not exempt drugs that were already on the market. Subsequent US laws that affect the FDA's review and approval of products include

- The Orphan Drug Act of 1983, which provides financial incentives to drug manufacturers to develop drugs for the treatment of rare diseases and conditions.
- The Prescription Drug User Fee Act (PDUFA) of 1992, which requires manufacturers to pay user fees to the FDA for new drug applications and supplements.
- The Dietary Supplement Health and Education Act (DSHEA amendment) of 1994, which removed from FDA the authority to require proof of safety

or efficacy prior to marketing of products considered dietary supplements (including herbal remedies). Only when a specific health claim is made by the product's manufacturer does the FDA have premarketing approval authority. Furthermore the FDA is required to determine that a product is unsafe to prevent sale and distribution.

- Section 112 of the Food and Drug Administration Modernization Act of 1997, which allows for an accelerated drug-approval process for agents to treat life-threatening illnesses.
- The Pediatric Research Equity Act of 2003 requires manufacturers to study, in children, drugs being submitted for approval for a claimed indication for which use in children is likely.

THE DRUG-DEVELOPMENT PROCESS

Figure 133–1 is a schematic overview of the process for drug development of a new molecular entity (NME).

Postmarketing Surveillance

The approval of every drug or medical device for marketing always carries with it some potential risk. Consequently, the FDA and the drug industry significantly rely on postmarketing surveillance for further safety data regarding the toxicity of a drug after approval. Individual pharmaceutical manufacturers are responsible for monitoring the safety of their products and reporting to the FDA, on a regular basis, any adverse events that were reported to them. The FDA's postmarketing

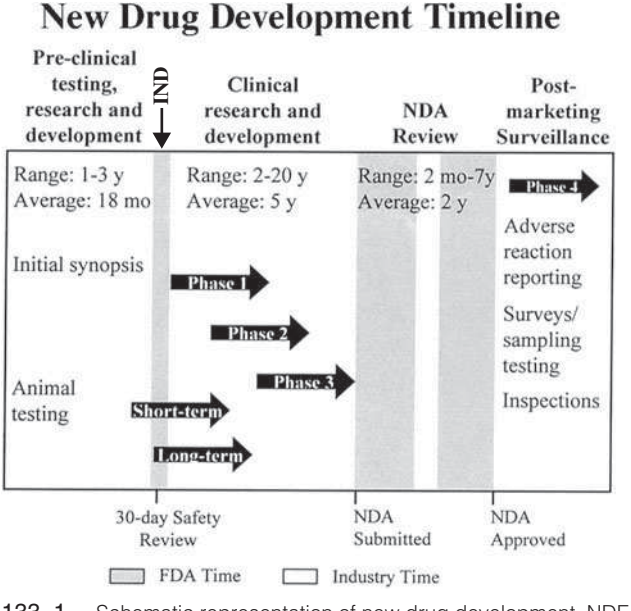


FIG. 133–1. Schematic representation of new drug development. NDE = new drug application. *(From www.fda.gov.)*

surveillance (MedWatch Program) for all medical products is a parallel system in place to monitor drug and medical device safety. The complete dataset is called the Adverse Event Reporting System (AERS database).

The FDA is primarily interested in the report of a serious adverse event, or an ADE previously not associated with the drug being administered, whether or not a causal relationship is established. An event is *serious* and should be reported when the patient outcome is one of the following:

- Death, if the death is suspected to be a direct result of the adverse event.
- Life-threatening, if the patient was considered to be at substantial risk of dying at the time of the adverse event or the use or continued use of the product would result in the patient's death (eg, gastrointestinal hemorrhage, bone marrow suppression, pacemaker failure).
- Hospitalization (initial or prolonged), if admission to the hospital or prolongation of a hospital stay resulted from the adverse event (eg, anaphylaxis, pseudomembranous colitis, or bleeding).
- Disability, if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's body function/structure, physical activities, or quality of life (eg, cerebrovascular accident caused by drug-induced coagulopathy and peripheral neuropathy).
- Congenital anomaly, if there are suspicions that exposure to a medical product before conception or during pregnancy resulted in an adverse effect on the child.
- Requires intervention to prevent permanent impairment or damage if use of a medical product is suspected to result in a condition requiring medical or surgical intervention to preclude permanent impairment or damage to a patient (eg, burns from radiation equipment requiring drug therapy, or breakage of an orthopedic screw requiring replacement of hardware to prevent malunion of a fractured long bone).

On occasion serious ADEs detected in the AERS database have led to the withdrawal of products from the US market without conducting additional studies. As a requirement for hospital accreditation, the Joint Commission on Accreditation of Healthcare Organizations mandates hospitals to collect, analyze, and report both significant and unexpected ADEs to the FDA.

The primary limitation of the MedWatch system is the exclusive reliance on spontaneous reporting of adverse events. Significant underreporting is known to occur in such systems. Current estimates are that fewer than 10% of ADEs are reported.

ESTABLISHING THE DIAGNOSIS OF DRUG-INDUCED DISEASE

The recognition and diagnosis of a drug-induced disease, or an ADE, is an essential skill for practitioners, including medical toxicologists and clinical pharmacists. The diagnosis of an ADE is typically made as a result of a systematic medical evaluation. One approach to making the diagnosis of drug-induced disease involves consideration of six related questions concerning the patient's clinical presentation and available medical data (Table 133–1).

EXAMPLES OF FDA REGULATORY ACTION BECAUSE OF SAFETY CONCERNS FOR DRUGS IN THE US MARKET

The past several years have seen drug withdrawals from the US market as a result of postmarketing recognition of ADEs in three general areas:

TABLE 133–1. Questions to Consider When Establishing the Diagnosis of an Adverse Drug Event

1. Was the timing of the adverse event appropriate relative to the exposure to the drug?
2. Has the effect noted, which is the suspected ADE, been reported before?
3. Is there evidence of excessive exposure to the drug?
4. Are there other more likely etiologies responsible for the condition suspected as being an ADE?
5. What is the patient's response to dechallenge?
6. What is the patient's response to rechallenge?

(a) prolongation of the QTc, (b) significant drug–drug interactions, and (c) hepatotoxicity.

Prolongation of the QTc

Three significant drug withdrawals in the mid to late 1990s exemplified a serious drug-safety issue with an agent found to prolong the QTc when administered alone or as the result of increasing plasma concentrations of the drug as a result of inhibition of its metabolism by other medications. The three examples in this category are terfenadine (Seldane), astemizole (Hismanal), and cisapride (Propulsid).

Significant Drug–Drug Interactions

Mibefradil (Posicor) is a prime example of a drug withdrawn from the US market because of postmarketing discovery of a plethora of drug–drug interactions. Mibefradil, a pharmacologically unique calcium channel blocker was approved by the FDA for the treatment of patients with hypertension and chronic stable angina. The FDA approved mibefradil for marketing in 1997, and at that time, information regarding its inhibition of hepatic cytochrome P450 (CYP) enzymes were known and printed on the drug label. The initial labeling for mibefradil specifically listed three drug–drug interactions: astemizole, cisapride, and terfenadine. During the first year that mibefradil was marketed, information accumulated regarding drug–drug interactions with many other agents as well. In an unprecedented step for a drug with numerous drug interactions, the FDA requested that it be withdrawn from the market. The FDA felt that the diversity of drug–drug interactions could not be addressed by standard drug label instructions and additional public warnings.

Drug-Induced Hepatotoxicity

A new drug application for bromfenac sodium (Duract), an NSAID, was submitted for review to the FDA in 1994 and after 28 months of review was approved. Because of a preapproval concern by the FDA that long-term exposure to bromfenac could cause hepatotoxicity, bromfenac labeling specified that the product was to be used for 10 days or less. This dosing limitation appeared to be in conflict and logically inconsistent with the initial approved drug indication for treatment of a chronic condition (eg, osteoarthritis). In February 1998, approximately 6 months after approval for marketing, the FDA amended the drug label for bromfenac sodium with a special "black box" warning indicating that the drug should not be taken for

more than 10 days and emphasizing the risk of severe hepatitis and liver failure. Severe injury and death from long-term use of bromfenac sodium continued to be reported, and, ultimately, the sponsor agreed to voluntarily withdraw bromfenac sodium from the market in June of 1998.

Other Examples of Postmarketing Safety Problems Leading to Drug Withdrawal

One voluntary withdrawal of two separate drugs used in combination serves as an example of the discovery and publicizing of an unusual adverse event occurring years after individual drug approval but after a significant increase in the prescription use of the combination product. The drug fenfluramine was approved in 1973 after an FDA review period of 75 months. Clinical investigation of a similar agent, dexfenfluramine, began in 1991 in the United States with approval of its IND. The new drug application for this product was filed in 1993, and after 35 months of review the drug was approved for marketing in 1996. A significant increase in prescription use of a combination product of fenfluramine with phentermine (referred to as "fen-phen") began to occur in the 1990s, when clinical data suggested that this drug combination was effective in a weight-loss program. Dexfenfluramine was approved for weight loss as a single agent for up to 1 year of use. Use of the fen-phen drug combination, however, was never fully approved by the FDA and was therefore considered an "off-label usage" of the product. In July 1997, research reported 24 cases of an unusual form of cardiac valvular disease causing aortic and mitral regurgitation in patients using the fen-phen combination.

THE ROLE OF THE TOXICOLOGIST IN THE DETECTION AND PREVENTION OF ADVERSE DRUG EVENTS

Medical and clinical toxicologists can have significant beneficial impact in ADE diagnosis and prevention in the areas of patient care, education, and administrative functions. In patient care, it is common for the medical toxicologist to be the first medical specialist to be consulted for a patient with a potential ADE. The medical toxicologist's active involvement in the clinical arena, especially in settings where the initial diagnosis of ADEs can be made, serves to provide an important role model: the medical or clinical toxicologist is an educator in the specialty to promote the detection and prevention of ADEs. Medical and clinical toxicologists occupy many different roles in clinical practice in the United States. An obvious role for the medical or clinical toxicologist is as educator in the academic setting of a medical school and affiliated teaching hospitals or a pharmacy school. The administrative functions that the medical or clinical toxicologist can perform could also beneficially impact on enhancing detection and prevention of ADEs. The main administrative functions that fall into this category include the reporting of ADEs and serving on hospital or health organization committees that oversee therapeutics (for example, the pharmacy and therapeutics committee).

ADEs are known to be significantly underreported in the United States. Reporting ADEs at the local (hospital) and national level (MedWatch) should be a priority for every clinician in all disciples. A well-documented, complete report to MedWatch made by a healthcare professional is given priority review by the Food and Drug Administration.

134 Medications, Errors, and Patient Safety

A variety of error-producing conditions and factors interfere with human performance; Table 134–1 lists some of the more common ones. Such errors often manifest as a simple slip of action, or execution failure, arising from distraction by something other than the task at hand.

THE MAKING OF SAFE MEDICATIONS

There is a widely held view that medications that are approved through the Food and Drug Administration (FDA) are generally safe, and that the FDA maintains close ongoing surveillance of drugs that are approved. The first is overly optimistic, and the second unrealistic. Prior to 1900 in the United States, there was no legal requirement for manufacturers to establish the safety of their products through testing, and there were no restrictions on the therapeutic benefit claims that could be made. Current regulations offer significant protection, but errors in prescribing and delivery commonly cause injury.

THE MEDICATING PROCESS

There are five stages in the sequence of ordering a medication to its delivery: prescription, transcription, dispensing, administration and monitoring. In a study of serious medication errors, 39% were found to occur at the prescribing stage, 12% at transcription, 11% at dispensing, and 38% at administration.

The more steps there are in any process, the greater the likelihood of error. If each step is executed correctly 99.5% of the time, there will be a 5% probability of failure in a 10 step process, with the probability proportionately increasing with an increased number of steps in the process. By the time there are 25 steps, excluding fatigue and other factors that affect performance, the probability of error will have reached 12%. Although the medicating process has only five stages, there are multiple steps within each stage, so the potential for error is high. Figure 134–1 describes the typical errors that occur at each stage in the process, together with prevention strategies.

ADVERSE DRUG EVENTS, ADVERSE DRUG REACTIONS, AND DRUG-RELATED MORBIDITY

The incidence of adverse drug events (ADEs) in hospitalized patients is estimated to range from 2–20% or higher. About 7000 deaths are attributed to medication errors annually in the United States. Thus far, most of the emphasis in improving medication safety has been directed at the preventability of ADEs, which (in contrast to adverse drug reactions [ADRs]) result from medication errors. The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defines a medication error as "…any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer."

An ADR is not a medication error. For example, if a patient with no known allergies is given a medication and subsequently develops a reaction to it, an ADR has occurred that was not considered foreseeable or preventable with

TABLE 134–1. Common Factors That May Affect Human Performance

Fatigue
Sleep deprivation/debt
Transitions of care
Interruptions
Distractions
Attentional capture
Motivation/morale
Work acuity/cognitive load
Workplace ergonomics
Resource availability (RACQITO)
Inexperience

RACQITO refers to Resource Availability Continuous Quality Improvement Trade-Off.
For further details on contributing factors to medication errors see Santell JP, Hicks RW, McMeckin J, Cousins DD: Medication errors: Experience of the United States Pharmacopeia (USP) MEDMARX reporting system. J Clin Pharm 2003;43: 760–767.

the information available. The World Health Organization generally defines an ADR as any noxious, unintended, and undesired effect of a medication that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding therapeutic failures, intentional and unintentional poisoning, medication abuse, and adverse events caused by medication administration errors or noncompliance.

The most frequently reported cause is *performance deficit* (43%), which is reported more than twice as often as the next most frequent cause, *procedure/protocol not followed* (20%). A performance deficit means that the individual making the error had the prerequisite knowledge to avoid the error but failed to do so. As noted above, there are numerous variables that contribute to performance deficit, including many ergonomic issues, such as workload, distractions, resource limitations, and staff shortages. The third and fourth most frequent causes were *documentation* (12%) and *knowledge deficit* (10%).

Significant costs are associated with an ADE. In 1997, excluding the cost of injury to patients or malpractice costs, the cost of one single ADE was estimated at $2000–$2500 and a preventable ADE at almost double that amount. The estimated annual cost of medication-related morbidity and mortality is more than $77 billion in ambulatory care, $2 billion in hospitals, and $4 billion in nursing home settings.

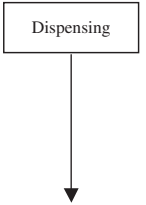
THE IMPACT OF AGE

There are important medication safety issues for children and the elderly. Both are generally underrepresented or excluded from clinical trials. It is estimated, for example, that only a third of the medications used to treat children have been adequately tested in this population. Similar concerns apply to medications used in the elderly.

Children

In one survey, the inaccuracy of home antipyretic use was estimated at almost 50%. In the emergency department setting, one study estimated the error rate at 10% of all charts. Generally, children in the intensive care unit appear to be

FIG. 134–1. Stages in the ordering and delivery of a medication, and typical errors associated with each stage.
[a]The Beers Criteria (sometimes also called the Beers List) highlights medications that are generally considered inappropriate in the elderly because of an unacceptable side effect profile. (See Fick DM, Cooper JW, Wade WE, et al: Updating the Beers criteria for potentially inappropriate medication use in older adults: Results of a US consensus panel of experts. Arch Intern Med. 2003;163:2716–2724.) *(continued)*



Dispensing	Dispensing by nurses Dispensing by physicians Patient ID	Nurses dispense to another nurse and not directly No dispensing by physicians Automated dispensing Check with physician if any ambiguity in order Check correct placement of decimal points Check weight is correct in kilograms Always check for allergies to medication class Doubly confirm patient identification; bar-coding Double-check arithmetic
Administration	Multiplicity of medications Potency of medications Multiple patients Parenteral administration Medication incompatibilities Physician administration	Be prepared to challenge orders Clarify any ambiguity or doubt concerning medication order Consistent consultation with reference materials Consultation with hospital pharmacist if available, or the PCL Call back verbal orders Implement systematic safety checks Avoid physician administration of medication whenever possible
Monitoring	Potent medications Parenteral administration Emergent procedures Complex procedures	Ensure adequate monitoring technology Ensure adequate monitoring personnel Clear protocols for conscious sedation or rapid sequence intubation Ensure adequate monitoring time following drug administration
Followup	Patients leaving hospital or other healthcare facility, and especially medicated patients	Reconcile all medications No verbal discharge instructions to patients given amnestic drugs Provide written information on any new medication to patient if possible Advise patients of any necessary follow-up Consider effect of medication if patient will be driving

FIG. 134–1. *(continued)*

at higher risk for errors, presumably reflecting the increased complexity of their disease and the medications used.

Children are vulnerable to medication errors for a variety of reasons. First, there are obvious communication difficulties. The patient does not play an active role in his or her medicating process, and the child is entirely dependent on adults. This dependency includes, of course, exposure to medications during pregnancy and lactation. Second, confusion sometimes arises over the child's weight. Third, the child's lower weight makes the child vulnerable for several reasons. In contrast to adults, weight-based dosing is necessary in children, which introduces an additional and critical step in the process. Also, there is often a requirement for dilution of stock medication in preparing the correct dose. Erroneously calculated dose and dosing interval make incorrect dosing the most commonly reported error. Fourth, there is an increased vulnerability of critically ill children to injury from medication, especially if the renal and hepatic systems are immature; children are three times more likely to suffer harm or death from a medication error compared with adults.

Older Adults

There are more than 1.5 million nursing home residents in the United States. The average resident uses six different medications, and 20% use ten or more. One model predicts that 350,000 ADEs occur annually in this group, more than half of which are preventable. Fatal or life-threatening ADEs represent 20,000 of these predicted events, of which 80% are preventable.

Advancing age brings with it three important considerations from the point of view of medication safety: (a) There is an increasing morbidity with age, and therefore an increasing likelihood of receiving a medication. (b) Frailty and cognitive decline in the elderly may result in errors in self-administration and may require the assistance of family members or others for proper medicating. (c) The majority of medications are developed and tested on healthy young people. Because the elderly are underrepresented, the slowing of metabolism, renal function deterioration, and a variety of other changes that result in altered pharmacokinetics are never adequately considered.

SOLUTIONS

Response to Medication Error

The leading cause of medication errors is human performance deficit. Invariably, a human action precedes the ADE, and this temporal contiguity of action and consequence inevitably generates a tendency to blame someone; this is usually the last person to have had contact with the patient. In recent years, however, a consensus has emerged that blaming people for errors is counterproductive.

Root cause analysis (RCA) is a term originally used to investigate major industrial incidents. Judiciously conducted RCA may provide insights into systemic failures underlying the ADE, and identify areas that require change. An alternative approach is failure mode and effect analysis (FMEA), which proactively attempts to identify errors that might occur, so as to implement preventive measures.

Human Factors Approach

As a general principle, it would be preferable if the dominant purpose in designing medical devices and processes was that they fit human users, and not

the converse. A particularly important goal is the reduction of cognitive load. The adoption of some very simple strategies based on human factors engineering principles will reduce error, such as simplification of the number of steps involved, reducing reliance on memory, applying cognitive forcing strategies, and using cognitive aids. One particularly useful aid is the color-coded Broselow-Luten system, which can be used for pediatric medication dosing.

Information Technology Innovations

Information technology (IT) in healthcare has been ponderously slow to develop, compared with its use in other organizations, but it is now gathering momentum and has obvious potential for improving patient safety. Computerized medication administration records can achieve significant reductions in administration and transcription errors. Further gains can be made by improvements of the interface between the laboratory and the pharmacy, and by ensuring that critical values can be transmitted simultaneously to the attending physician.

Ward-Based Clinical Pharmacists

Pharmacist participation at the clinical interface reduces medication errors, and prevents ADEs. The involvement of a clinical pharmacist in work rounds of an adult ICU reduced preventable ADEs by 66%, and reduced the serious medication error rate in the pediatric ICU to 20% of the prepharmacist rate.

Improving the Workplace

Working long hours, experiencing sleep deprivation, and incurring sleep debt are all known to compromise cognitive and psychomotor performance and are, undoubtedly, contributory factors in medication errors.

Education

The prevailing emphasis in physician training is on knowledge acquisition. Less time is spent inculcating critical thinking skills and teaching reasoning, the assumption being that these are passively acquired during the process of training. Many aspects of the medicating process are not formally taught during medical training. Importantly, communication theory should receive more emphasis in training. Good communication skills within and between disciplines, especially between practitioners and their patients, will limit errors.

As patients are admitted, transferred within, and discharged from healthcare facilities, there is an ongoing imperative to communicate exactly what medications, strengths, and doses they are receiving, and ensure that any changes are accurately recorded. This is the process of medication reconciliation and was adopted by Joint Commission on Accreditation of Healthcare Organizations in 2005 as one of its National Patient Safety Goals.

Improved Accountability of Medication Manufacturers

There are many ways in which pharmaceutical companies might improve medication safety. Initiatives are already under way to ensure the appropriate naming and preparation of medications to minimize confusion.

135 Risk Management and Legal Principles

Patients who are experiencing toxicologic emergencies require immediate care, yet are often unable to give informed consent because their impaired consciousness prevents them from making decisions. Treating patients who present with confusion and are irrational or who manifest dangerous behavior is extremely difficult. Clinicians must recognize the medical–legal problems created when the impaired patient refuses treatment or admission to the hospital and insists on leaving against medical advice. No clear guidelines are available to the physician confronted with such a toxicologic emergency. There is no nationally recognized standard of law relating to these issues; the relevant laws vary from state to state. The legal requirements of informed consent, the duty to treat, medical malpractice, battery, and negligence are examined here, and guidelines based on generally accepted common law principles. In addition, New York State case law and statutes are suggested for developing appropriate patient care plans and departmental policies.

INFORMED CONSENT

Deciding to medically treat an individual against the individual's will poses a difficult problem. Even if justified, forcible treatment violates a patient's autonomy, and an individual's right to privacy.

A patient's right to choose his or her own course of medical treatment was first recognized in the early 19th century in a landmark case decided by the US Supreme Court, *Schloendorff v Society of New York Hospital*. The court stated:

> Every human being of adult years and sound mind has a right to determine what shall be done with his own body and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages, except in cases of emergency where the patient is unconscious and where it is necessary to operate before consent can be obtained.

This includes the right to refuse care, as well as the right to terminate care already in progress. In a nonemergent situation, it is the physician's responsibility to obtain approval from the patient or the patient's surrogate before rendering treatment.

Generally accepted components to the informed consent process consist of (a) an explanation of the treatment/procedure, (b) alternative choices to the intervention, and (c) relevant risks, benefits, and uncertainties to each alternative. Furthermore, it is the duty of the physician to assess how well the patient understands the above information.

Courts recognize that the requirement for informed consent is not absolute, and that there are exceptions in which a physician does not need to obtain permission before rendering treatment, especially in emergency situations. Situations are generally considered emergent if a patient's care would be compromised if there were a delay in treatment. In New York, an emergency is defined as a situation that includes either the immediate endangerment of life or health or the need for the immediate alleviation of pain. Often a physician's well-intended efforts to communicate treatment information to an im-

paired patient prove ineffectual and present the practitioner with a medical–legal dilemma. The physician is unable to discuss in a meaningful way the implications of the proposed treatment with the patient; nevertheless, there is a duty to treat a patient who presents with a life-threatening condition or the potential for permanent disability. In these situations, consent on the part of the impaired patient is considered to be implied, and emergent treatment should be provided.

RISK MANAGEMENT CONSIDERATION AND DOCUMENTATION

The problems associated with an improperly documented emergency department record are numerous, but they can be minimized if the practitioner is cognizant of risk-management principles. The physician is required to write a medical record that amply supports the basis for the medical judgments exercised. Inappropriate entries or markings on the medical record can weaken the defense in a liability case. If a physician must correct a prior entry made on the record, the preferable method is to draw a single line through the value or word to be changed, insert the correct information directly above, and initial the correction. Dating the correction also precludes potentially difficult questions of timing and responsibility in a courtroom setting.

Any documentation supporting the restraint of an impaired patient against his will must include a clinical description to support such a forcible impediment to the patient's right to liberty and freedom of movement. Such a clinical description should specifically describe any manifestation of agitation and uncooperative behavior. The record should refer to the specific uncooperative acts of the patient, and, most importantly, should comment on the difficulties in providing care to the patient because of the patient's actions. Physicians who order restraints for patients must exercise extreme caution in the language used to describe such patients. As a general rule, all healthcare professionals should depict a compassionate and professional manner by describing patient behavior and life styles in objective clinical terms.

FORCIBLE RESTRAINT OF THE IMPAIRED PATIENT

The right of a hospital to retain and physically restrain a person who has an altered level of consciousness for evaluation and emergency intervention is generally well supported by state and case law. A decision to allow a treated or partially treated patient with a drug overdose who subsequently becomes alert to return to the community must be based on an assessment of several factors. The initial concern is the patient's capacity to comprehend. Before the patient can be permitted to leave the hospital, a determination has to be made that the patient is capable of understanding the information presented and has neither a medical nor a psychiatric problem preventing such a voluntary decision. The next consideration is to assure that the person is medically stable. Documentation of these elements is an essential requirement of sound medical practice.

ALCOHOL AND EVIDENCE

The judicial system has historically been one of the most effective tools to combat drunk driving, and its effectiveness depends on the ability to identify and punish individuals who violate the laws. It is essential, however, that the collection of evidence does not violate the rights afforded by the United States Constitution. Every state, as well as the District of Columbia, has

driver "implied consent" laws. When a person obtains a driver's license, he or she consents at the time of acquisition to a chemical alcohol test if suspected of driving while intoxicated. Under the implied consent laws, when a person suspected of driving while intoxicated refuses to take an alcohol test, he or she is then subject to a penalty. Specific penalties for refusals vary from state to state. At a minimum, the refusal results in suspension or revocation of a driver's license. Certain states, for example, Texas and Illinois, allow blood tests to be performed on patients as ordered by a law officer, when there is probable cause that driving while intoxicated resulted in severe injury, whereas other states, such as New York and California, allow forced blood samples with a warrant issued by a judge. State laws regarding the approach to this situation vary and it is important that the emergency department staff be familiar with the specific requirements of the law of that state.

Laws and regulations governing the seizure of blood for the purpose of blood alcohol testing generally require the procedure be (a) done in a reasonable, medically approved manner, (b) be incident to a lawful arrest, and (c) be based on the belief that the arrestee is intoxicated. These laws and regulations vary from state to state and are the subject of frequent restructuring and amendment. It is recommended that medical staff review with hospital counsel the local laws and regulations that pertain to these issues.

CONFIDENTIALITY

The Health Insurance Portability and Accountability Act (HIPAA) was created to increase the portability of health insurance and allow employees to maintain insurance when they changed jobs. During the 1990s, the weaknesses of the existing medical records system gained attention as multiple high-profile breaches of confidentiality surfaced. Thus the HIPAA Privacy Rule was created to govern the use and disclosure of protected health information in the hands of healthcare providers, health plans, and healthcare clearinghouses. The HIPAA Privacy Rule was not intended to impede healthcare. Physicians have the freedom to consult with each other, in their own institution and outside, for the purpose of providing clinical care. Additionally, there are several specific exceptions to the Privacy Rule listed within the document—situations where protected health information may and often must be disclosed, and may be disclosed without an individual's permission. For example, activities related to public health, such as reporting communicable diseases, information necessary to report actual or suspected abuse, neglect, or domestic violence, or information pertaining to cadaveric organ or tissue donation are specifically exempt from the Privacy Rule. The HIPAA Privacy Rule specifically addresses consultations with poison centers. It states: "We consider the counseling and followup consultations provided by poison control centers with individual providers regarding patient outcomes to be treatment. Therefore, poison control centers and other healthcare providers can share protected health information about the treatment of an individual without a business associate contract."

LEGAL CONSIDERATIONS FOR POISON CENTERS AND INFORMATION SPECIALISTS

Telephone Contact with a Poison Information Specialist

As a general rule, any physician who decides to treat a patient enters into a physician–patient relationship that creates well-established legal duties. Courts

have ruled that the physician–patient encounter need not be a face-to-face interaction to have legal consequences. For example, the absence of a physical contact between a physician and patient, as in the practice of radiology and pathology, does not preclude a patient from asserting that a duty of care exists. More particularly, and quite relevant to the practice of a poison center, a New York State court ruled that an initial telephone call from a patient to a physician can be sufficient basis to hold that physician responsible for inappropriate advice or a significant error in judgment.

Practices of Regional Poison Centers That Can Reduce Potential Liabilities

To minimize the risk of legal actions against a poison center, quality assurance and risk-management programs are essential. Daily physician audits or monitoring of the advice given by poison information specialists should be done. Such interactions enhance care and ensure patient safety for the individual and establish a higher general standard.

The medical toxicologists and clinical pharmacists responsible for supervising the poison information specialists must be able to adequately assess the competence and capabilities of the staff and to make recommendations, take corrective actions, and provide suggestions for improvement. This process is facilitated by such actions as audiotaping calls made to the poison center and the subsequent advice given, and reviewing written records maintained by the information specialist on each particular case. Documentation is extremely important, because in the event of a lawsuit, the most likely area of dispute will be what was actually said to the patient or physician calling for advice.

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