REVIEW ARTICLE

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Salicylate Toxicity

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On presentation to the emergency department, patients with fever, tachypnea, rales on lung examination, and acid–base disturbances are often given a suspected diagnosis of viral infection, yet persons with salicylate toxicity may present with similar symptoms. This article highlights the risk factors for salicylate toxicity; reviews the pathophysiological effects; notes the hidden sources of salicylates, including foods, drugs, and topical ointments, that if used in combination may result in unintended toxic effects; and discusses treatment strategies. Especially during the current pandemic, clinicians should be aware of the potential for salicylate poisoning,[1] which occurred in the 1918–1919 pandemic of Spanish influenza.[2]

Background and Epidemiology

Use of salicylates as therapeutic agents dates back more than 3500 years, when it was recognized that the bark of the willow tree possessed analgesic and antipyretic properties. In 1838, the Italian chemist Raffaele Pirìa produced salicylic acid from salicin, the medically active ingredient in the willow. His student Cesare Bertagnini later reported the onset of a continuous noise in his ears, now recognized as tinnitus, after voluntarily ingesting approximately 6 g of the compound over a period of 2 days.[3] An unstable form of acetylsalicylic acid was chemically synthesized for the first time by the French chemist Charles Frédéric Gerhardt in 1853. Subsequent work during the second half of the 19th century defined the chemical structure and established efficient methods of synthesis, ultimately leading to registration of the drug under the name Aspirin by Friedrich Bayer and Company in 1899.[3]

Salicylates are found in a myriad of prescription and over-the-counter medicinal preparations, including acetylsalicylic acid tablets and analgesic mixtures. Methyl salicylate (oil of wintergreen), found in topical liniments and solutions used in hot vapors, is the most concentrated form of salicylate: 1 ml of a 98% solution contains 1400 mg of salicylate.[4] A large amount of salicylate (8.7 mg per milliliter) is also found in bismuth subsalicylate, which is sold as a generic medication under the brand name Pepto-Bismol. The widespread availability, ease of access, and frequent coingestion of multiple salicylate-containing agents, combined with the nonlinear pharmacokinetic properties of salicylate, make salicylism a common and sometimes fatal occurrence (Fig. 1). On the basis of data from 2014 through 2018, approximately 25,000 exposures to acetylsalicylic acid are reported annually to poison control centers in the United States.[8,9] In 2018, acetylsalicylic acid alone was involved in 17,380 cases of salicylate poisoning, with unintentional exposure more common than intentional exposure.[9] Moderate or severe toxic effects occurred in 1761 of the 17,380 cases; 26 additional patients died. Given the wide range of signs and symptoms and the high rates of death and complications as-

sociated with a toxic overdose of salicylate, clinicians need to be well versed in diagnosing and treating salicylate poisoning.[10]

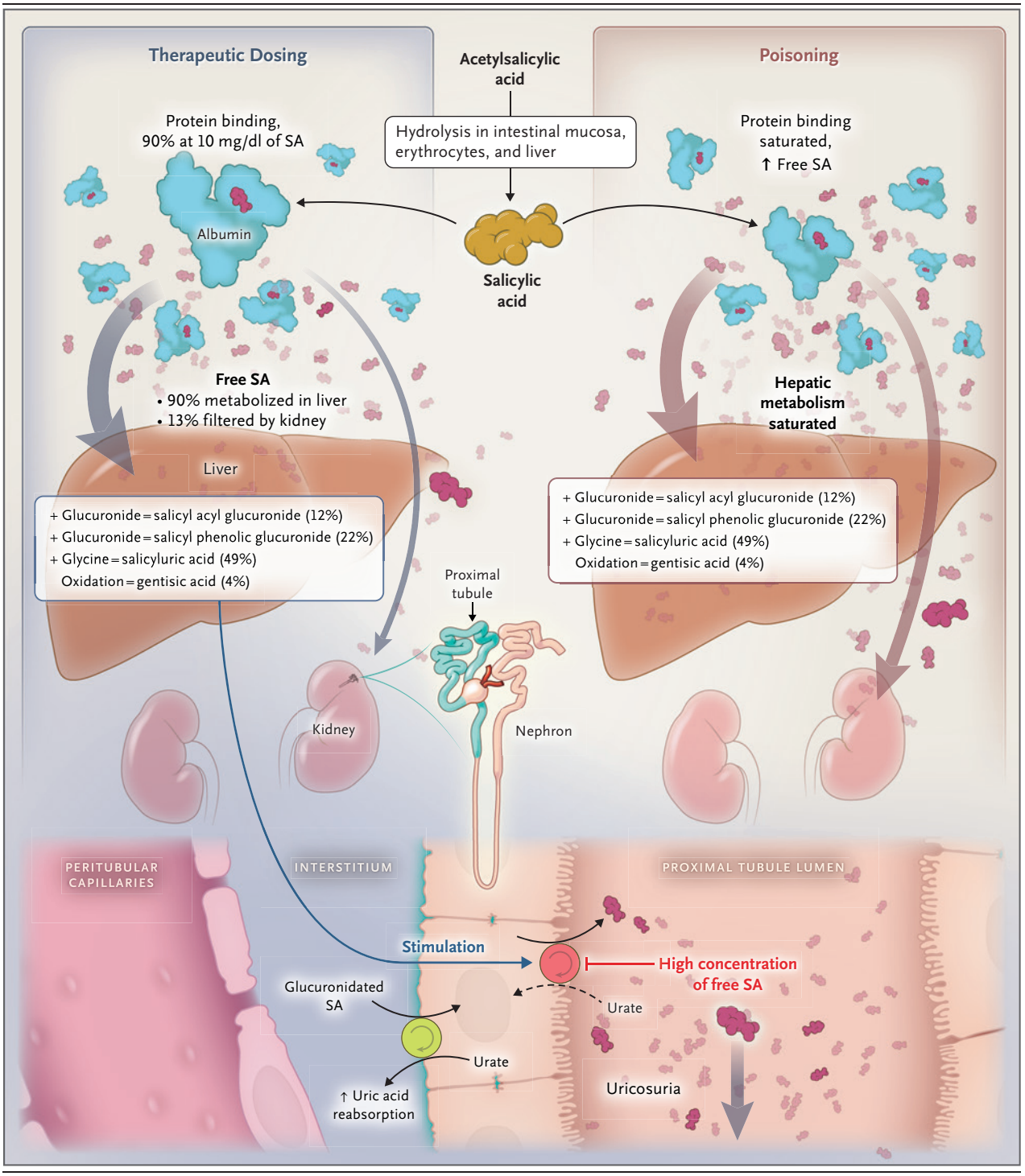
ACUTE VERSUS CHRONIC SALICYLATE INTOXICATION

Salicylate poisoning is characterized as either acute or chronic. The acute form of salicylate intoxication generally occurs in young adults who have a psychiatric history or who have had a previous overdose. Such persons tend to ingest salicylate alone or in combination with other drugs in a suicide attempt; when they present to the emergency department, they frequently volunteer that they have ingested salicylate or are found with partially filled containers of the drug, making the diagnosis straightforward. Within 1 or 2 hours after a single salicylate ingestion, at which point plasma levels often exceed 40 or 50 mg per deciliter (2.9 or 3.6 mmol per liter; levels between 15 mg per deciliter [1.1 mmol per liter] and 30 mg per deciliter [2.2 mmol per liter] are considered to be therapeutic for inflammatory conditions), clinical manifestations of salicylate intoxication include tinnitus, vertigo, nausea, vomiting, and hyperpnea.[11] Plasma levels between 50 mg per deciliter and 70 mg per deciliter (5.1 mmol per liter) indicate severe intoxication and can be associated with fever, sweating, listlessness, and incoordination. At levels exceeding 75 mg per deciliter (5.4 mmol per liter), patients are at risk for hallucinations, seizures, cerebral edema, coma, noncardiogenic pulmonary edema, and cardiovascular collapse.

The time of ingestion of salicylate, the plasma level, and clinical toxicity are only loosely correlated. Coingestion of ethanol or opioids and the effects of high doses of salicylate itself slow gastric emptying and delay the peak concentration of the drug.[12,13] Slow absorption of enteric-coated formulations and multiple acetylsalicylic acid ingestions that are separated in time may result in a disconnect between clinical manifestations and plasma levels.[14,15] Frequent monitoring is required, and an undetectable or low salicylate level should not lull the clinician into complacency about the need to initiate treatment if the assessment suggests a possibility of salicylism.

A chronic form of intoxication may occur in patients who are ingesting acetylsalicylic acid therapeutically and then have an inadvertent overdose. Since the baseline tissue burden of the drug is high and pathways for salicylate elimination are nearly or fully saturated, additional intake of the drug may lead to substantial accumulation of free salicylate and extension of the normal half-life of 2 to 4 hours to as long as 20 hours.[16] The plasma level of salicylate required to elicit symptoms tends to be lower in chronic than in acute salicylate poisoning, sometimes falling into the upper end of the therapeutic range, because of the large amount of drug previously distributed to and located within tissues, including the central nervous system (CNS). In cases of acute salicylate toxicity, rising plasma levels are roughly correlated with the development of expected clinical manifestations, but such correlations are notoriously absent with chronic toxicity. Overreliance on drug levels can lead to underestimation of the severity of poisoning and delay implementation of appropriate therapy, potentially contributing to worse outcomes. Serum (or plasma) levels should be used as an adjunctive consideration, along with the severity of the presenting symptoms, presence or absence of acid–base disorders, and overall clinical condition of the patient.

Chronic poisoning is more common in elderly patients, who often are cared for by more than one clinician and therefore are at risk for inadvertent dual prescribing. Use of nonprescription drugs (e.g., cold remedies and stomach remedies) as therapy for symptoms of associated medical problems or in a misguided attempt to relieve symptoms can lead to accidental intoxication. A particularly high-risk scenario is simultaneous use of an oral salicylate-containing drug, topical application of a methyl salicylate–containing cream along with a heating pad, and home remedies containing herbs and spices enriched with salicylate.[17,18] Heat induces skin pores to open and disperses the cream across a greater surface area, enhancing systemic absorption. If the cream comes in contact with irritated skin — or epithelium that has compromised integrity — systemic absorption is further enhanced. Naturally occurring foods and food additives contain salicylates; the highest concentration is found in herbs and spices. For example, ingestion of ginger or mint tea as part of a home remedy can add to the drug burden.[19,20] Lack of awareness that such substances contain salicylate explains why pa-



tients may not know that they have ingested salicylates. Preexisting kidney disease or a salicylate-induced decrease in kidney function can contribute to increased plasma levels. Administration of a drug that unbinds salicylate from protein, particularly in a patient with chronic kidney disease and hypoalbuminemia, can also increase the free salicylate level and lead to toxic effects.

The diagnosis of acute intoxication is generally straightforward, but chronic salicylate poisoning can be difficult to diagnose, in part because

Figure 1 (facing page). Salicylate (SA) Metabolism under Conditions of Therapeutic Dosing and Toxicity.

Acetylsalicylic acid is a prodrug with a short half-life (approximately 20 minutes) because of rapid hydrolysis to salicylic acid by serine esterases in the intestinal wall, erythrocytes, and liver.[5,6] As the plasma level of acetylsalicylic acid falls, there is a rapid rise in the salicylic acid level. Both acids are weak — the negative logarithm of the acid dissociation constant (pK_a) for acetylsalicylic acid is 3.5 and for salicylic acid is 3.0 — and at physiologic pH exist primarily in the ionized form (SA). SA is mainly metabolized by the liver into its glycine conjugate, salicyluric acid, and its glucuronic acid conjugates, salicyl phenolic glucuronide and salicyl acyl glucuronide. These products are excreted by means of organic anion transporters in the proximal tubule of the kidney, where they can compete for uric acid excretion. Only about 10% of unchanged SA is freely excreted by the kidney. The pathways of hepatic metabolism are readily saturable and have nonlinear kinetics such that a fixed amount of SA is eliminated per unit of time independent of the drug concentration. As a result, increased doses of acetylsalicylic acid cause the plasma SA level and apparent half-life to progressively increase. SA normally circulates bound to albumin in the plasma, but with increasing total plasma SA levels, the unbound fraction increases. Free SA is then filtered by the glomerulus, where high concentrations on the luminal side of the proximal tubule inhibit uric acid absorption. This process explains the paradoxical effect of SA on kidney urate excretion: at low doses, urate excretion is decreased, whereas at high doses, urate excretion is increased.[7]

Table 1. Initial Diagnosis in Patients Subsequently Found to Have Chronic Salicylate Poisoning.

Encephalopathy of undetermined origin[10,21-24]
Dementia or delirium
Viral encephalitis
Unexplained asterixis
Cardiopulmonary disease[10,23,25]
Impending myocardial infarction
Pneumonia
Acute alcohol intoxication, alcohol withdrawal, or alcoholic ketoacidosis[23,26]
Sepsis[27,28]
Diabetic ketoacidosis[26]
Unexplained decrease in capacity for self-care[26]

there is no clear history of excess ingestion. Although clinical findings overlap, classic symptoms and signs tend to be milder or absent in cases of chronic toxicity and may in fact be attributed to other disease processes or the ailment that was being treated (Table 1). Age-related decreases in hearing acuity may attenuate the perception of tinnitus or its cause. Tachypnea and rales on pulmonary examination may be attributed to preexisting lung and cardiac disease as opposed to salicylate-induced noncardiogenic pulmonary edema. Hyperpyrexia and altered mental status can be mistaken for sepsis, and metabolic acidosis accompanied by circulating ketone bodies may be ascribed to diabetic or alcoholic ketoacidosis.

Neurologic abnormalities, such as agitation, confusion, hallucinations, slurred speech, seizures, and coma, occur more frequently in patients with chronic salicylate poisoning than in those with acute intoxication. "Salicylate jag" refers to restlessness and mental aberrations that are reminiscent of alcohol intoxication. In one series, 60% of patients underwent intensive neurologic investigation, which delayed the diagnosis of salicylism for up to 3 days after admission.[10] Delays in diagnosis and therapy account for the higher morbidity and mortality associated with chronic intoxication than with acute intoxication. A high level of suspicion for chronic salicylate intoxication is needed in evaluating at-risk patients who have tachypnea, acid–base disturbances (particularly an unexplained respiratory alkalosis), and nonfocal neurologic abnormalities and in elderly patients who have a deterioration in activities of daily living with no known cause. Even in the absence of a documented history of ingestion, plasma levels should be measured if salicylate intoxication is suspected.

PATHOPHYSIOLOGY

Toxic levels of salicylate exert a direct stimulatory effect on the respiratory center of the medulla, causing an increase in the rate and depth of respiration and the development of respiratory alkalosis. Salicylates also uncouple oxidative phosphorylation and inhibit citric acid cycle dehydrogenases, causing a shift in metabolism to glycolysis for energy production[29] (Fig. 2). A compensatory increase in body catabolism and substrate breakdown is required to supply the energy needed for the increasingly inefficient production of ATP from ADP through glycolysis. This response is manifested by increased oxygen consumption, increased heat production (leading to hyperpyrexia, diaphoresis, and dehydra-

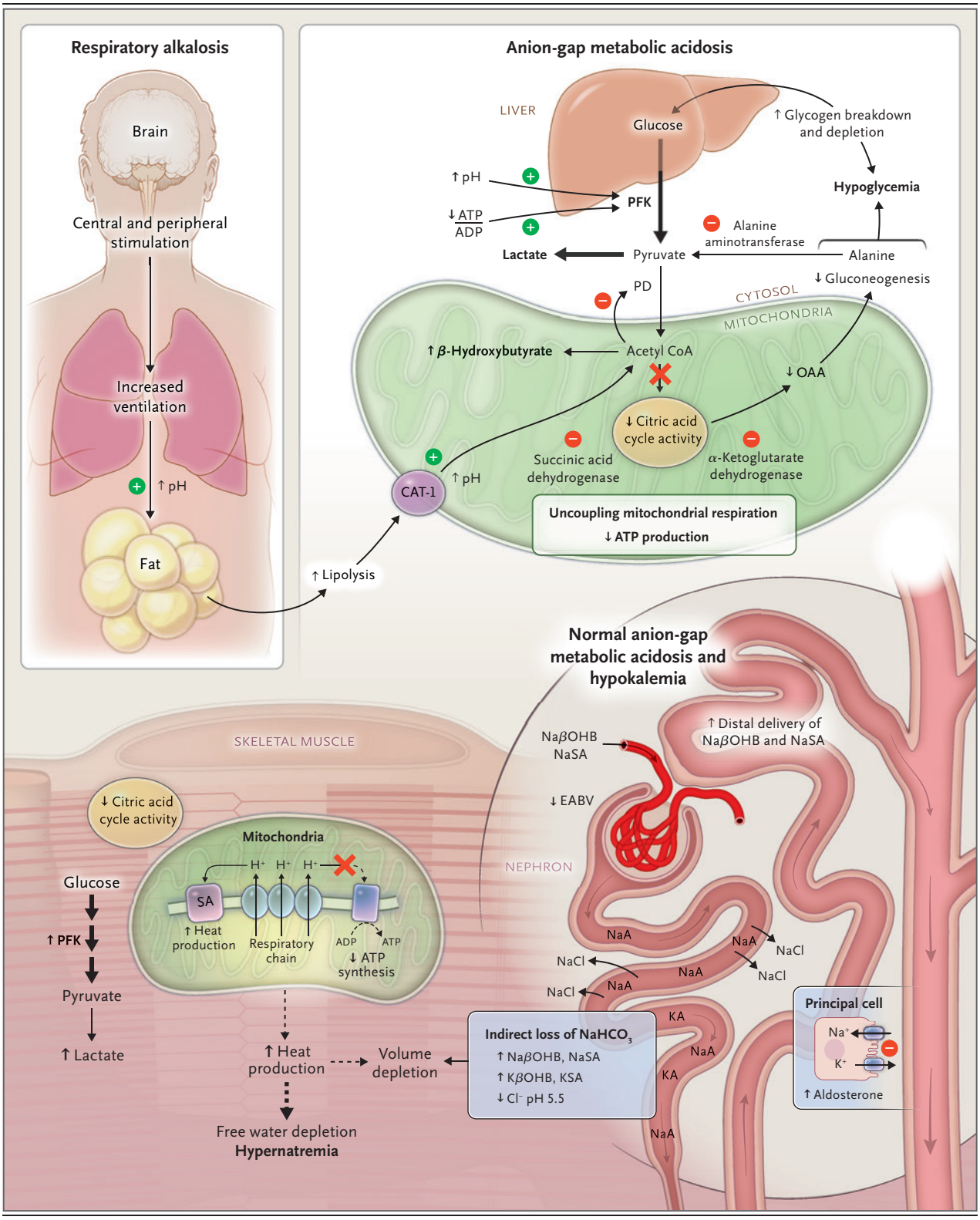


Figure 2 (facing page). Mechanisms of Acid–Base Disturbances in Salicylate (SA) Toxicity.

SA poisoning has initial stimulatory effects on peripheral chemoreceptors, followed by direct effects in the central nervous system, which result in increased respiration and lead to respiratory alkalosis.[30] At the same time, aerobic production of ATP is reduced as a result of an ionophoric effect of SA in the mitochondria, causing uncoupling of oxidative phosphorylation combined with decreased activity of the citric acid cycle because of inhibitory effects on succinic acid dehydrogenase and α-ketoglutarate dehydrogenase.[30-33] Increased pH and low intracellular ATP lead to anaerobic production of ATP through stimulatory effects on the rate-limiting enzyme phosphofructokinase (PFK), which activate glycolysis. Increased pH also contributes to increased ketogenesis through stimulatory effects on hormone-sensitive lipase, leading to increased lipolysis and facilitating the entry of fatty acids into the mitochondria by decreasing the inhibitory effect of malonyl–coenzyme A (CoA) on carnitine palmitoyltransferase.[34,35] Lactate and ketoacid production are primarily responsible for the increase in the anion gap. Excretion of sodium and potassium salts of acids in the urine, combined with retention of chloride, leads to a normal anion-gap acidosis. Increased distal delivery of sodium salts in the presence of increased aldosterone leads to potassium wasting and hypokalemia. Hypoglycemia can develop as a result of depleted glycogen stores combined with lack of substrate availability for gluconeogenesis because of decreased citric acid cycle activity and decreased conversion of alanine to pyruvate due to inhibitory effects on alanine aminotransferase.[36-38] CAT-1 denotes carnitine acyltransferase 1, EABV effective arterial blood volume, KA potassium anion, KβOHB potassium β-hydroxybutyrate, KSA potassium salicylate, NaA sodium anion, NaβOHB sodium β-hydroxybutyrate, NaSA sodium salicylate, OAA oxaloacetate, and PD pyruvate dehydrogenase.

tion), depletion of liver glycogen, and increased metabolic production of carbon dioxide. Although it is not common, neuromuscular irritability manifested as paratonia and extreme muscle rigidity can develop, further contributing to hyperthermia and increasing the risk of rhabdomyolysis.[39-41] The accumulation of ketoacids and other organic acids accounts for the majority of the increase in the anion gap. The contribution of salicylate is minor (<5 mmol per liter). Increased renal bicarbonate excretion in response to respiratory alkalosis decreases buffer capacity, potentially worsening the degree of acidosis as organic acids accumulate (Fig. 2).

LABORATORY ABNORMALITIES

More than half of patients with salicylate poisoning have a mixed respiratory alkalosis and increased anion-gap metabolic acidosis.[42] Most affected adults who have ingested salicylates alone present with an alkaline pH, whereas coingestion of drugs that depress the CNS blunts the hypocapneic response. In one series, respiratory acidosis was present in 23% of patients who had ingested salicylates in combination with other drugs, as compared with only 2% of patients who had ingested salicylates alone.[42] A pure respiratory alkalosis occurs in 20 to 22% of patients. An acid pH is more common in infants and young children because of an inappropriate adaptive respiratory response to the metabolic acidosis.[43] The anion gap tends to be higher when respiratory alkalosis is dominant, which is consistent with an alkaline pH–associated increase in both lactate and ketoacid production. In a rodent model of salicylate intoxication, production of these acids is minimized when inspired carbon dioxide is increased to prevent salicylate-induced hypocapnia.[44]

Approximately 20% of patients have a hyperchloremic normal anion-gap acidosis,[42] which can be the result of several mechanisms. First, increased excretion of bicarbonate accompanied by retention of chloride is a compensatory response of the kidney to respiratory alkalosis.[45] Second, urinary excretion of sodium and potassium salts of organic acids is the equivalent of losing sodium bicarbonate from the body. The resultant contraction of extracellular fluid volume signals renal retention of dietary sodium chloride.[46,47] Third, concomitant ingestion of bromide-containing compounds will lead to a false elevation in the plasma chloride level, since both bromide and chloride are halides.[48] Finally, an increased plasma salicylate level can cause autoanalyzers to falsely report an increased plasma chloride level, leading to an erroneously low or even negative value for the anion gap.[49]

Although respiratory alkalosis facilitates the production of organic acids, it can ameliorate the toxic effects of salicylate on the CNS by slowing the entry of salicylate into tissues. Since salicylic acid has a pK_a (negative logarithm of

the acid dissociation constant) of 3, an alkaline blood pH ensures that more than 99% of the drug is in an ionized state, for which cell membranes are poorly permeable. The nonionized fraction of salicylic acid readily penetrates cells and will double in concentration if blood pH falls from 7.4 to 7.2. As a result, a greater amount of drug will leave the extracellular fluid, and intracellular concentrations will be increased in the brain, liver, and other organs.[50] This shift can be confusing when patients are being treated for salicylate poisoning, since the toxic effects may worsen at a time when plasma levels of the drug are decreasing. A risk factor for a drop in pH is coingestion of drugs that depress the CNS, causing decreased respiration.

Other fluid and electrolyte disturbances can develop in patients with salicylate poisoning. Patients with severe intoxication may have fluid deficits of 4 to 6 liters. Hypernatremia can develop as a result of accelerated, insensible water loss in the lung due to increased ventilation, and increased metabolism and heat production lead to cutaneous water loss from sweating. Salicylate-induced emesis and urinary excretion of sodium organic acid salts cause the total-body sodium content to be reduced. Excretion of these salts also causes renal potassium wasting and hypokalemia due to increased delivery of sodium to the distal nephron at a time when mineralocorticoid levels are increased.[51] High salicylate concentrations in the tubular lumen interfere with urate reabsorption in the proximal tubule, causing severe hypouricemia. In the early stages of toxicity, transient or prolonged hyperglycemia can develop as a result of the combined effect of increased production of glucose and decreased use of glucose by tissues. However, depletion of glycogen stores and impaired gluconeogenic pathways confer a predisposition to hypoglycemia, particularly in patients with chronic intoxication or the later stages of acute intoxication[52,53] (Fig. 2). CNS hypoglycemia may be present even with normal peripheral-blood glucose levels.[54]

TREATMENT

There is no specific antidote for salicylate poisoning. The initial approach is to perform a rapid clinical assessment and initiate supportive therapy, with particular attention to ensuring adequate respiration and stabilizing the circulation. Early consultation with a toxicologist is recommended. Endotracheal intubation can lead to deleterious effects in patients with severe salicylate poisoning and should be considered only when clinical evaluation and blood gas analysis indicate hypoventilation.[55] The brief period of apnea associated with endotracheal intubation can lead to a rapid fall in pH, causing increased amounts of the drug to accumulate in the CNS through protonation of salicylate.

Aggressive volume resuscitation is required in patients with hypotension and decreased extracellular fluid volume. Lactated Ringer's solution or isotonic saline can be administered at a rate of 10 to 20 ml per kilogram of body weight per hour for the first 2 hours, with subsequent adjustment to maintain a urine output of 1 to 1.5 ml per kilogram per hour (Table 2). Patients should be reassessed at frequent intervals, with appropriate adjustment of fluid administration if there are signs of cerebral or pulmonary edema. The goals of fluid therapy are to establish euvolemia and not force diuresis, which has been associated with an increased risk of pulmonary edema.[56] Some patients with chronic salicylate poisoning have a presentation similar to that of sepsis, with persistent hypotension despite fluid resuscitation. In such patients, vasopressor therapy is required for blood-pressure support.

Cardiopulmonary stabilization is followed by therapy to decrease gastrointestinal absorption of any remaining drug and initiation of measures to enhance removal from the body (Table 2). Activated charcoal is effective in inhibiting absorption of orally administered salicylate and should be given if the patient is alert and cooperative, regardless of the time since ingestion.[57] Activated charcoal is most effective if given within 2 hours after salicylate ingestion. Ingestion of large quantities of aspirin, which slows gastric emptying, and the use of enteric-coated or sustained-release tablets are risk factors for prolonged retention of the drug in the gastrointestinal tract and justify use of activated charcoal, even in patients who present more than 2 hours after ingestion.[58,59] In one study, intoxicated patients were found to have large amounts of acetylsalicylic acid in the stomach up to 9 hours after ingestion. The dose of activated charcoal can be repeated every 4 hours until charcoal appears in the stool and clinical manifestations of salicylate intoxication are re-

Table 2. Treatment of Salicylate Poisoning.*

Treatment	Rationale or Indications	Dosing and Treatment Considerations	Comments
Activated charcoal	Gastrointestinal decontamination	1–2 g/kg of body weight to maximum of 100 g in adults; 1 g/kg to a maximum of 50 g in children†; multiple-dose treatment is most effective for bezoars and for enteric-coated or sustained-release preparations	Most effective if given within 2 hr after ingestion; sorbitol often given with first dose, but repeated use is discouraged because of exacerbation of electrolyte disturbances and abdominal cramping; risks include vomiting, corneal abrasion, and aspiration, particularly in patients with altered mental status and unprotected airway; multiple-dose treatment can decrease plasma SA and capture SA that desorbs along the gastrointestinal tract
Whole-bowel irrigation‡	Gastrointestinal decontamination	Polyethylene glycol through nasogastric tube at a dose of 20–40 ml/kg/hr until rectal effluent is clear (usually 4–6 hr)	Consider when SA levels do not respond to activated charcoal alone, suggesting bezoar formation or ingestion of enteric-coated or sustained-release preparations
IV fluids			
	Restoration and maintenance of extracellular fluid volume; forced diuresis not recommended because of risk of pulmonary edema	Lactated Ringer's solution or isotonic saline: 10–20 ml/kg/hr until a urine flow of 1–1.5 ml/kg/hr is established	Lactated Ringer's solution may be preferable, since normal saline can cause normal anion-gap acidosis and lower pH
	Alkalinization of urine until SA level is <40 mg/dl (2.9 mmol/liter), plasma pH has normalized, metabolic acidosis has resolved, and patient is asymptomatic with normal respiratory rate and effort; oral bicarbonate is not a substitute, since it can increase SA absorption by enhancing dissolution of tablets in intestinal lumen	Initial IV bolus of 1 mmol of HCO_3^-/kg, followed by continuous infusion: 3 ampules of $NaHCO_3$ (1 ampule contains 44 mmol of $NaHCO_3$) added to 1 liter of D5W, with goal to keep urine pH >7.5; infusion rate of 1.5 to 2 times the maintenance dose for IV fluids is usually sufficient; 40 mmol of potassium chloride can be added, in absence of acute kidney injury and oliguria, to treat hypokalemia; dextrose (0.5–1 g/kg bolus) can reverse acute delirium	Initiate alkalinization in all symptomatic patients with SA levels above therapeutic range and in suspected cases pending measurement; respiratory alkalosis is not a contraindication; monitor with serial ABG studies to avoid systemic pH >7.5; hypokalemia is common because of urinary losses and can worsen with alkalinization; hypoglycorrhachia can occur with normal plasma glucose level
Extracorporeal SA removal	Indications: severe signs or symptoms, including severe fluid and electrolyte disturbances, cerebral edema, acute respiratory distress syndrome, and acute kidney injury, regardless of SA level; plasma SA level >90 mg/dl (6.5 mmol/liter), regardless of signs or symptoms, or >80 mg/dl (5.8 mmol/liter) if kidney function is impaired	Conventional hemodialysis is preferred, but hemoperfusion or continuous arteriovenous hemodiafiltration is an acceptable alternative if hemodialysis is not available; urine alkalinization is not required during hemodialysis and can be restarted after the procedure if patient is symptomatic or SA level is pending	Multiple hemodialysis treatments may be required if the gastrointestinal burden of the drug is large, which can cause continuous absorption
Mechanical ventilation	Endotracheal intubation when respiratory efforts are faltering, to protect airway in obtunded or delirious patients; sedation for dialysis-access placement	$NaHCO_3$ at a dose of 2 mmol/kg to improve plasma pH before intubation	Avoid decrease in ventilation, since decrease in pH will enhance movement of salicylate into tissues and precipitate clinical deterioration; experienced provider has the best chance of first-pass success

* ABG denotes arterial blood gas, D5W 5% dextrose in water, HCO_3^- bicarbonate, IV intravenous, $NaHCO_3$ sodium bicarbonate, and SA salicylate.
† In vitro studies have shown that each gram of activated charcoal can adsorb approximately 550 mg of SA. A dose of activated charcoal by weight that is 10 times the weight of ingested acetylsalicylic acid is often recommended, but this may not be practical, since ingested amounts may exceed 20 to 30 g; thus, the maximum dose is 100 g in adults.
‡ Whole-bowel irrigation is contraindicated in patients with intestinal perforation, ileus, persistent vomiting, or gastrointestinal bleeding.

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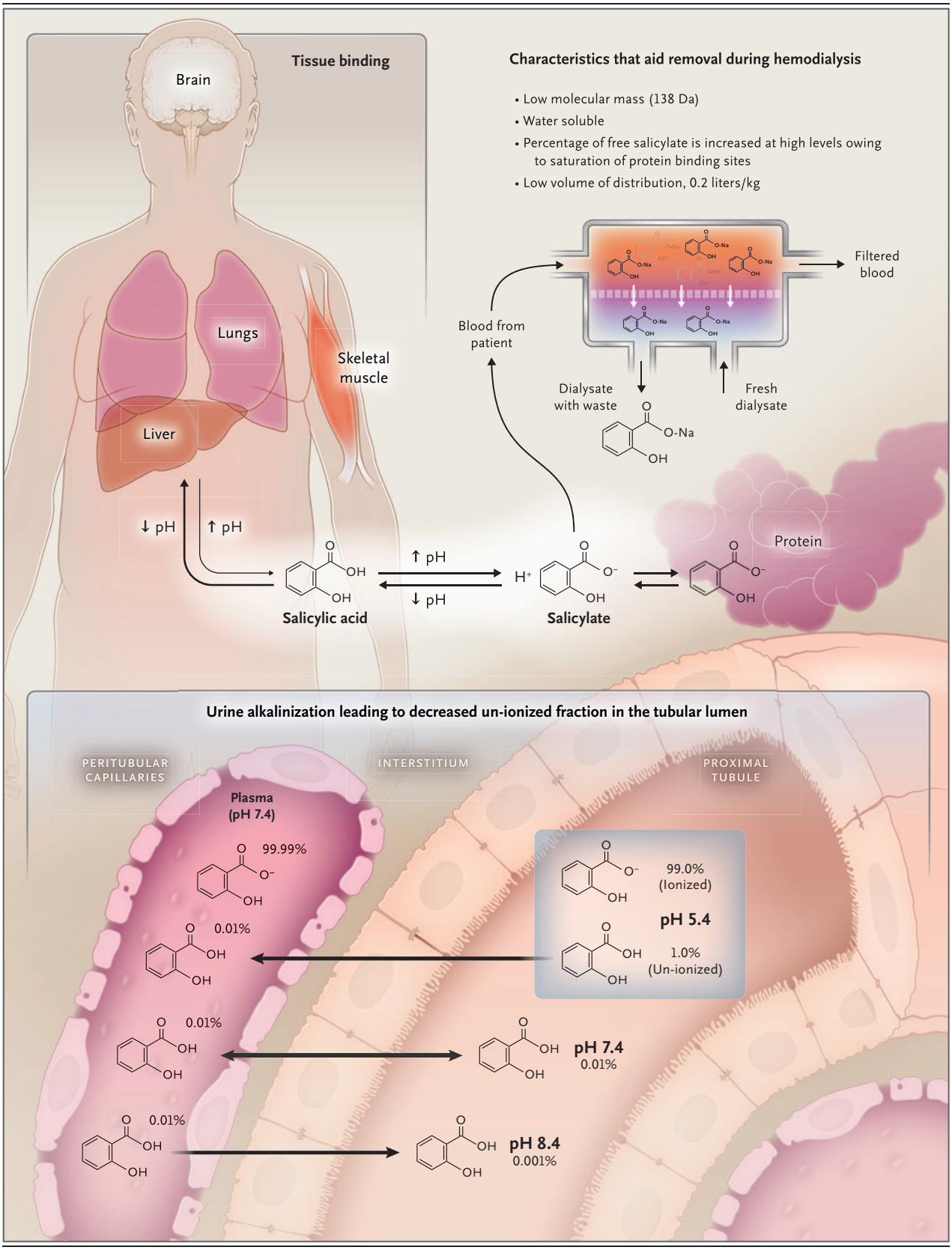

Figure 3 (facing page). Therapeutic Strategies to Remove Salicylate from the Body.

Alkalinization of the plasma with respect to tissues favors movement of salicylate out of tissues, and it then becomes trapped in the plasma. The reverse occurs with acidemia, which explains why clinical toxic effects can worsen when the salicylate level is decreasing. Urinary excretion of salicylate is markedly pH-dependent. Acidic urine favors protonation of salicylate, increasing its solubility and enhancing absorption by the tubules. In contrast, as the urinary pH rises from 5 to 8, the amount of free ionized salicylate excreted increases logarithmically from 3% of the total salicylate dose to more than 80% through ion trapping in the urine. Salicylate has characteristics that make it readily removed during hemodialysis.

solving. Repeated doses may lower plasma salicylate levels and may be particularly useful in treating bezoars, which should be suspected when salicylate levels continue to rise or fail to decrease, despite appropriate management. In such cases, whole-bowel irrigation with polyethylene glycol may also be useful.[60,61] Additional doses of activated charcoal can capture salicylate that desorbs from the charcoal initially given.[58] A risk of aspiration (due to altered mental status or increasing somnolence), poor gastric motility, and salicylate-induced gastrointestinal hemorrhage are contraindications to the use of activated charcoal.

Alkalinization of the urine to accelerate kidney clearance of salicylate is essential in the management of both acute and chronic intoxication.[62] Salicylate is filtered at the glomerulus and undergoes both reabsorption and secretion by the proximal tubule. When urine pH is less than blood pH, the undissociated salicylic acid is partially reabsorbed by nonionic diffusion. Conversely, ionized salicylate is trapped in the tubular lumen when the urine pH is greater than the blood pH. Increasing the urine pH from 6.1 to 8.1 will increase the clearance of salicylate by a factor of 18. This therapy also alkalinizes the plasma, decreases the amount of circulating lipid-soluble salicylate, and promotes movement of the drug out of the CNS (Fig. 3). An initial bolus of 1 mmol of sodium bicarbonate per kilogram, followed by a continuous infusion of 5% dextrose in water containing sodium bicarbonate (3 ampules, each containing 44 mmol of sodium bicarbonate added to 1 liter of solution), is a reasonable strategy for alkalinizing the urine. The infusion rate is adjusted to keep the urinary pH above 7.5. Bicarbonate therapy should be given to alkalinize the urine even when respiratory alkalosis predominates over metabolic acidosis, but it is reasonable to avoid raising the arterial pH above 7.5. A potential complication of this therapy is a decrease in the plasma ionized calcium level, leading to tetany. The infusion can be discontinued once the plasma salicylate level is reduced to a therapeutic level in association with an improvement in the clinical manifestations. Oral bicarbonate is contraindicated, since raising the gastrointestinal luminal pH can accelerate the dissolution of remaining tablets, causing increased salicylate absorption.

Hypokalemia is often present and can be made worse with an alkaline diuresis, particularly if the patient has not had adequate volume resuscitation. Increased delivery of sodium (coupled to bicarbonate) to the distal nephron in patients with increased mineralocorticoid levels will increase potassium secretion. If urine output is adequate and there is no evidence of acute kidney injury, 40 mmol of potassium can be added to each liter of solution to help correct the deficit. Deficits should be corrected, since hypokalemia increases the expression of hydrogen–potassium–ATPase in the collecting duct, making it more difficult to establish an alkaline urine.[63]

Acetazolamide decreases bicarbonate reabsorption in the proximal tubule by inhibiting carbonic anhydrase, resulting in a bicarbonate-rich alkaline urine. However, this approach is associated with a risk of inducing systemic acidemia. In addition, acetazolamide can increase plasma salicylate levels by displacing salicylate from protein binding and interfering in tubular salicylate secretion.[64]

Hemodialysis is the most efficient way to remove salicylate from the body. The small size, low volume of distribution, and absence of tissue binding make salicylate an ideal substance for dialysis (Fig. 3). Salicylate is protein-bound at therapeutic levels but is largely free at toxic levels. Dialysis can also correct the acidosis, other electrolyte abnormalities, and volume disturbances induced by salicylate poisoning. The threshold for starting hemodialysis should be lower for patients with altered mental status or renal insufficiency, patients with the acute respiratory distress syndrome who require supplemental oxygen,

and those in whom standard therapy has failed, regardless of the salicylate level.[65-67] Alkalinization of the urine should be initiated but is not a substitute for hemodialysis in such patients. A plasma salicylate level of more than 90 mg per deciliter (6.5 mmol per liter) is an indication for dialysis, regardless of signs and symptoms. This threshold for initiation of dialysis is particularly important in patients with acute poisoning after salicylate ingestion, since there may be few signs or symptoms in the first several hours after ingestion. Prompt removal of the drug at this stage can limit tissue accumulation and avert severe toxic effects. Continuous venovenous hemofiltration or hemodiafiltration can be used if the patient's hemodynamic condition is unstable or if conventional hemodialysis is unavailable.[68]

SUMMARY

Salicylates are found in numerous substances that can be ingested together, inadvertently leading to life-threatening toxic effects. Clinicians are reminded that many of the signs and symptoms of salicylate poisoning mirror those of viral infections, including coronavirus disease 2019 (Covid-19), as well as other conditions.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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