The use of atropine in a nerve agent response with specific reference to children: are current guidelines too cautious?

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Accepted 30 November 2008

ABSTRACT

This review examines the potential use of nerve agents by a terrorist organisation against a civilian population, which has become an increasingly apparent threat in the UK. Present guidelines for the use of atropine, particularly in children, following such an event are unclear. No precise agreement exists on the most appropriate dose of atropine, or the frequency with which it should be administered. This uncertainty leaves children vulnerable as potentially life-saving treatment may be crucially delayed. Guidelines must be standardised to allow rapid antidotal delivery and maximise the potential for survivors. This review examines the issues currently surrounding the use of atropine in children following a nerve agent attack and propose strategies for treating exposed children.

Concern over the potential use of nerve agents by terrorists against a civilian population has risen in recent years, particularly since the Japanese attacks in the 1990s.[1] Medical countermeasures available in the UK in the event of such an attack must be considered. Guidelines for the management of adults following nerve agent exposure have been published, and a combination of atropine, pralidoxime and diazepam is well recognised as the most appropriate treatment.[2–4] The optimum management of children, however, remains unclear. After being commissioned by the Health Protection Agency (HPA), we reviewed the current literature on the use of atropine in a nerve agent attack, and from this developed guidelines for treating exposed children.

METHODS

We conducted a systematic literature search for all relevant articles using Medline (1950–2008), Embase (1980–2008), Cinahl (1987–2008) and the National Library of Medicine's Pubmed database. Search criteria included (''exp.chemical warfare agents/'' or ''exp.organophosphorous compounds/'' or ''nerve adj agent$.af'') and ''exp.atropine/'', with limits set to English and human. This search was repeated with additional search criteria of ''infant/'' or ''child, preschool/'' or ''child/'' or ''adolescent/''. All references generated were analysed by two reviewers to select those references relevant to the topic. References were selected as relevant if they discussed the clinical effects of nerve agent exposure in either adults or children, as very few data exist on the effect of nerve agents in children alone. With respect to management and the use of antidotes, only those references including a discussion on atropine were included, with articles solely on the use of oximes excluded.

A second independent literature search using similar criteria was conducted by the HPA and identified an additional three references. Two references from the ''closed'' literature were also included. Advice from the British National Formulary was included and the internet search engine Google was used to identify websites of agencies who provide advice on the management of casualties following a nerve agent attack (two references).

Pathophysiology of nerve agents

Nerve agents are organophosphorous anticholinesterase compounds. They are inexpensive to manufacture, can be dispersed relatively easily and are difficult to detect.[2 3 5] They cause inhibition of the enzyme acetylcholinesterase and as acetylcholine accumulates at neural junctions causing overstimulation of both muscarinic and nicotinic receptors, a cholinergic crisis ensues (table 1).[6–9] A direct effect on the central nervous system (CNS) may also occur causing convulsions, altered conscious level or coma.

Nerve agents are liquids under temperate conditions but are likely to be aerosolised or vaporised in an explosion, with exposure most likely via inhalation or dermally.[3] Victims may experience symptoms of vapour inhalation within seconds and death can ensue in seconds to minutes. If removed from ongoing exposure the effects usually peak within 15–30 minutes and if the casualty survives this initial period, the chances of overall survival are high. Skin exposure is more variable and can result in more delayed effects, with symptoms occurring within anything from seconds to up to 18–24 h.[2] Miosis is the hallmark clinical sign of exposure to organophosphorous compounds in adults, but children may present with more prominent CNS signs.[10] Respiratory failure is the primary cause of death, however, as the patient experiences bronchorrhoea, bronchoconstriction and central apnoea.

The aim of atropine treatment

The primary goal of atropine therapy is to control the bronchorrhoea and prevent respiratory failure. Atropine acts as a competitive antagonist at muscarinic cholinergic receptors in the central and peripheral nervous system and reverses the muscarinic, but not the nicotinic, symptoms of acetylcholine overstimulation. Pralidoxime acts by breaking the nerve agent–anticholinesterase bond and aims to restore normal activity of the anticholinesterase enzyme, while diazepam is an anticonvulsant but

Table 1 Clinical effects of nerve agent exposure

Muscarinic	Miosis
	Bronchoconstriction
	Glandular hypersecretion
	Bradycardia
	Gastrointestinal hypermotility
Nicotinic	Fasciculations
	Weakness
	Flaccid paralysis
	Tachycardia
Central nervous system	Convulsions
	Loss of consciousness
	Apnoea

also has a neuroprotective role in reducing the cerebral morphological damage potentially caused by nerve agents.[11]

In the event of a nerve agent attack causing mass casualties, treatment should ideally be directed towards those in which it will be most effective. Children exposed to nerve agents are likely to fall into three broad categories: (1) those who succumb rapidly to the lethal effects; (2) those who demonstrate only mild effects and are in no way incapacitated and (3) those who fall between these extremes, exhibiting symptoms but not quickly succumbing to death. Treatment will probably be too late to be effective in the first group, and may not be required for those with very mild effects. The greatest benefit will therefore probably be observed in children displaying symptoms but not quickly succumbing to death. Through directing treatment towards this group of patients, respiratory failure may be prevented to allow decontamination and evacuation.

Clinical presentation in children

The diagnosis and management of nerve agent exposure relies on clinical judgement, with syndrome recognition and the provision of immediate resuscitation and antidotal treatment. There may be clues to the diagnosis as multiple victims are likely to have been affected rapidly, often in a confined space. It has been proposed that children may be disproportionately affected, and present with a different clinical picture, as a result of differing physiological and behavioural characteristics.[2 6 12 13] A child's smaller mass but relatively larger body surface area has been suggested to result in a lower dose of nerve agent being required to cause clinical effects following skin exposure. With a higher respiratory rate, minute volumes and metabolic rate, children have been suggested as being likely to inhale a greater dose of nerve agent than an adult at a given concentration. Similarly, they have been considered by some to be more vulnerable to the effects of a cholinergic crisis as a result of smaller airway diameters, relative nose breathing and anatomical subglottic narrowing. CNS depression with hypotonia, rather than muscarinic symptoms, may be a more prominent early feature as the nerve agent is thought to penetrate a child's blood–brain barrier more easily than an adults.[2 6] Some agents with higher vapour pressures (eg, sarin) are thought to concentrate close to the ground with greater risk to shorter children.[14] This is difficult to confirm, however, and in a genuine nerve agent attack many adult casualties are likely to be lying on the ground and therefore exposed to a similar degree. Behavioural aspects such as a child's understanding or ability to follow protective instructions may, however, leave them more vulnerable to the effects of the nerve agent.

Dose of atropine

A number of recommendations for the dose of atropine in children exposed to nerve agents have been identified that will lead to a variation in the time to full atropinisation (table 2).[15] The dose should be large enough to achieve a rapid clinical effect both for the benefit of the patient and to assist decisions about future doses. The dose used in symptomatic bradycardia in children (usually 0.02 mg/kg) is also the current paediatric dose recommended by UK sources for use after nerve agent exposure, with the dose repeated every 5–15 minutes until atropinisation is achieved.[16 17] Data extrapolated from adults suggest that this may not be effective quickly enough, however, as previous experience with organophosphorous pesticide poisoning has shown that up to 30 mg of atropine has been required in the first few hours of therapy.[2 6] In nerve agent poisoning, when the overall dose of active drug absorbed will be somewhat less than in ingestion of pesticide concentrates, doses of atropine are likely to be intermediate between these extremes.

Many of the current guidelines are based on military studies performed in non-nerve agent-exposed personnel with features of significant atropinisation used as an endpoint. Military autoinjector Mark 1 kits, containing 2 mg atropine and 600 mg pralidoxime, are therefore frequently advised for use in civilian adults exposed to nerve agents. The use of an autoinjector device is believed to result in broader drug dispersion and increased rate of absorption than would be achieved with a needle and syringe.[18] A specific paediatric autoinjector device has recently been introduced, which, in contrast to the adult device, contains only atropine and no pralidoxime.[15 19 20] The licensed dose with the device is 0.5 mg for children weighing 15–40 lb and 1.0 mg for those weighing 40–90 lb, with no licence for use in infants and toddlers weighing less than 15 lb. Some organisations (eg, the US National Centre for Disaster Preparedness) have reservations over specific paediatric devices as they contain no pralidoxime and are not licensed for use in all children.[15 19] It is not clear why pralidoxime has been excluded from this paediatric device as it is believed to play a vital role in adequate antidotal therapy. The mark 1 combination device is therefore often advised for both adults and children, accepting that doses of atropine administered may be high in very young children. This raises the issue of the safety of excess atropine in children. Experiences of children in the Gulf War, accidentally injected with atropine autoinjectors, demonstrate that although they received doses up to 17-fold higher than standard doses for age, no fatalities or life-threatening arrhythmias among the 240 children who presented to hospital were reported.[21] Furthermore, Kozer *et al*[22] reported data collected from 142 cases of accidental self-injection with autoinjectors containing atropine and trimedoxime among Israeli children. Whereas 15% of children received doses higher than recommended, none experienced significant side effects. These data are thus reassuring for emergency responders using standard adult antidote kits.

Route of atropine delivery

The intravenous or intramuscular routes are commonly advised for atropine administration following a nerve agent attack. Although intravenous atropine is the ideal route as hypoperfusion following nerve agent exposure may reduce the bioavailability of intramuscular atropine, the intramuscular route is often advised in emergency due to ease of rapid delivery with an intramuscular autoinjector device, particularly with the use of personal protective equipment (PPE).[2] Historical military evidence, however, indicates the relative benefits of subcutaneous atropine in providing a more rapid clinical response than

Table 2 Paediatric nerve agent atropine autoinjector dosage comparison table

Organisation	Age in years	Weight in kg	Autoinjector	Dose
CDC	0–2	0–12	?	0.05–0.1 mg/kg
	2–10	12–30	0.5–1 Mark 1	1–2 mg
	>10	>30	1–2 Mark 1	2-4 mg
CPEM	<2	0–12	1 Mark 1	>0.17 mg/kg
	2–7	12–24	1 Mark 1	0.17–0.08 mg/kg
	8–13	25–49	2 Mark 1	0.16–0.08 mg/kg
	>14	>50	3 Mark 1	<0.12 mg/kg
NCDP	<3	0–13	1 Mark 1	>0.13 mg/kg
	3–7	13–25	1 Mark 1	>0.13–0.08 mg/kg
	8–14	26–50	2 Mark 1	0.13–0.08 mg/kg
	>14	>50	3 Mark 1	<0.12 mg/kg
AAP	1–6	>10	1 PedAtropJr	0.5 mg
	6–12	>20	1 PedAtrop	1 mg
	>12	>40	1 Mark 1	2 mg

AAP, American Academy of Paediatrics, Paediatric Terrorism and Disaster Preparedeness Resource; CDC, Centres for Disease Control and Prevention, United States Department of Health and Human Services; CPEM, Centre for Paediatric Emergency Medicine, USA; NCDP, National Centre for Disaster Preparedness, Columbia University Mailman School of Public Health, New York. Table adapted from Foltin *et al*, 2006.[15]

intramuscular administration (H Cullumbine, *et al*, 1953, unpublished observations). The mean time of occurrence to maximal pulse rate in soldiers given 1 mg atropine via the intravenous, subcutaneous and intramuscular routes was 7.3 minutes, 22.6 minutes and 62.5 minutes, respectively. Little is known, however, about the bioavailability of subcutaneous atropine, particularly in children. One cannot necessarily assume that it would be the same as adults, however, as a result of differences in subcutaneous fat, volume to body mass ratio or metabolic rate.

The intraosseous route is a method favoured when intravenous access is not possible in paediatric resuscitation. Although similar doses of atropine to those administered intravenously have been advised via this route, no data are available on intraosseous atropine following nerve agent exposure.[19] Nevertheless, use of this route should be considered as a practical alternative as it can provide rapid vascular access to allow fluid and drug administration, even in the presence of PPE.[23 24] There is also a lack of specific data on the use of endotracheal atropine in this situation. Many sources advise that if intubation is required, atropine may be delivered via this route. Data on efficacy are lacking and the effects of nerve agents are so fast that delays while the patient is electively intubated make this approach impracticable.

Pharmacokinetic data

Pharmacokinetic data should inform the debate on the initial loading dose of atropine through giving an indication of the expected time to peak effect (table 3). The challenge is to attain rapid "full" atropinisation without inducing toxicity by over-enthusiastic repeat dosing. Atropine has a variable volume of distribution of 1–6 l/kg and plasma concentrations correlate well with dose.[25] With little paediatric data much of the information has been extrapolated from adult studies. Peak serum concentrations in adults occur in 15–30 minutes after the intramuscular injection of 0.02 mg/kg atropine.[25–29] Although this time frame appeared to correspond with a peak in heart rate, the primary goal of therapy is to prevent death from respiratory failure due to bronchorrhoea. Antisialogogue effects are therefore likely to be a pharmacologically more appropriate endpoint for assessment. Initial antisialogogue effects are noted within 5 minutes, but peak effects are not seen for 45–60 minutes after intramuscular injection, with a similar delay noted in peak body temperature.[25 27 28 30] As nerve agents can have a dramatic clinical effect in seconds to minutes, a faster antidotal response would be required than that expected from an intramuscular atropine injection at the lower end of the dose range. Furthermore, most expert resources state repeated doses should be continued at 2–10 minute intervals until the resolution of secretions and bronchorrhoea.[2 15 31 32] Such recommendations are generally based on intravenous administration as given the intramuscular time profile illustrated this would run the risk of precipitating delayed atropine toxicity.

Other military studies have examined the onset of the effect of atropine when given in combination with pralidoxime and a benzodiazepine precursor. In one case plasma concentrations were measured in adult volunteers, but in the majority pulse rate was used as a marker of atropinisation. To complicate interpretation further, some studies involved doses of atropine 15 minutes apart. Co-administration with a benzodiazepine makes interpretation of pulse rate data difficult, and no proper measure of salivation was attempted other than subjective symptoms of dry mouth. These show peak plasma levels at 10–30 minutes after intramuscular dosing (three peak concentrations at 10 minutes; four at 20 minutes; two at 30 minutes) and a delay in onset of self-reported dry mouth (one at 20 minutes; four at 30 minutes; five at 45 minutes), and pulse rate change (peak 67 minutes) in line with the data quoted above.[33] Co-administration of pralidoxime did not obviously alter atropine absorption rate.[33]

DISCUSSION

The effects of a nerve agent attack against a civilian population have already been demonstrated and the threat of such an attack in the UK must be appreciated. Guidelines for emergency responders must be straightforward to allow rapid provision of potentially life-saving treatment. Many guidelines rely on the ability of the emergency responder, who may have limited paediatric experience, to assess symptom severity and the age or weight of the child accurately. Some have proposed the use of a length-based, colour-coded resuscitation tape to allow estimation of body weight, but the use of such an instrument would delay the delivery of treatment by up to 30 s and the extra time required to administer what may be a more accurate dose is probably not justified.[15] Concerns have also been raised that responders may have difficulty deciphering between unexposed

Table 3 Illustrative pharmacokinetic data available on intramuscular atropine in adults and children

Study	Dose	Route	Peak concentration	Peak HR	Maximum antisialogogue effects	Peak temperature (rectal)
Adults						
Berghem *et al*[29]	1 mg	IM	30			
Kentala *et al*[25]	0.02 mg/kg	IM	15	30	60–120	
Children						
Gervais *et al*[27]	0.02 mg/kg	IM	25	25	45	
Saarnivaara *et al*[28]	0.02 mg/kg	IM	30	30		60 minutes

This table indicates the time in minutes to peak concentration, peak heart rate (HR), maximum antisialogogue effects and peak rectal temperature in the pharmacokinetic studies available on atropine given intramuscularly (IM).

crying infants and those in respiratory distress, and faced with this decision treatment may be critically delayed. Although this raises the potential of administering atropine to an unexposed child, the risks of withholding treatment from exposed children are far greater. Emphasis should remain on quick assessment and delivery of the antidote, acknowledging that whereas some unexposed children may receive treatment unnecessarily, previous experience is reassuring in suggesting that they are relatively resistant to atropine toxicity.

Atropine is most readily bioavailable following intravenous injection, with subcutaneous atropine being intermediate and intramuscular atropine being the least efficient with respect to the speed of onset. Obtaining intravenous access in multiple casualties at speed, while using PPE may, however, be difficult. Consequently, the intramuscular route has been favoured traditionally, primarily as a result of the ease of rapid self-administration in the battlefield.[33] Whereas there is evidence to support the use of autoinjectors over a needle and syringe,[18] there is no scope for self-administration of an antidote in the civilian setting. Further consideration of subcutaneous atropine as a faster alternative to the intramuscular route is required. Current military autoinjectors are not designed for subcutaneous use but autoinjectors using this route are available in other clinical settings, eg, insulin administration. Before considering this as a viable alternative to the intramuscular route, however, further work is required to investigate the bioavailabilty of subcutaneous atropine, particularly in the shocked patient. The intraosseous route is another alternative that may prove easier to use than the subcutaneous route for the rapid delivery of atropine while using PPE. However, no pharmacodynamic or kinetic data on this route in this scenario exist in the open literature. While some have described the securing of vascular access to be more rapid with the intraosseous route, particularly in the presence of PPE,[23] this route may not be suitable for delivery of repeated doses that most sources advise until atropinisation is achieved. In addition, there are as yet no published data on bioavailability and the time frame of atropine effect following intraosseous dosing upon which to base further detailed recommendations. Ultimately, rapid decontamination with the securing of intravenous access is the gold standard and whichever method assists in achieving this is favourable.

Present protocols advocate repeat dosing with lower dose intramuscular atropine every 5–10 minutes until a clinical response is observed. With intramuscular doses of 1 mg taking up to an hour for full clinical effect in adults,[25 33] this suggests that the current recommended doses are too cautious and repeat dosing will render the patient at risk of delayed atropine toxicity while awaiting a clinical response. Indeed, when comparisons are made with studies of insecticide-poisoned patients, atropine requirements in those exposed to nerve agents appear to be higher than expected and drug doses found in autoinjectors are more consistent with initial than total doses of atropine.[32 34] These data, in conjunction with those demonstrating the relative safety of atropine in children, reinforce the validity of a protocol advocating higher initial dosing in an effort to ''front-load'' the patient with atropine. Furthermore, atropine bioavailability appears to be unaffected by combination with pralidoxime and benzodiazepine precursors. To achieve optimum protection following a nerve agent attack on civilians, atropine should be combined with pralidoxime and a benzodiazepine. Ideally, doses should be standardised for all children in an effort to prevent delays while emergency responders assess the child's age and weight. If guidelines for both adults and children can be agreed across all agencies then responders are left in little doubt as to the most appropriate management so that potentially life-saving treatment can be provided without delay.

CONCLUSIONS

The use of atropine alone in a first response to nerve agent exposure is likely to produce a suboptimal clinical benefit and oximes should be co-administered whenever possible to minimise ageing of cholinesterase.

The initial dose of atropine should be sufficient to achieve rapid atropinisation to control the bronchorrhoea and prevent respiratory failure.

The intramuscular route is likely to remain the first choice, although the intraosseous route, as advised as an alternative to the intravenous route in paediatric resuscitation, requires more consideration.

Use of repeat dosing under present guidelines appears to run the risk of excess late atropinisation as further doses will be given before pharmacokinetic data suggest a full onset of effect. In contrast, there are data indicating that children are relatively resistant to the adverse effects of atropine overdose in this scenario, enabling larger initial doses to be justified.

We suggest a higher initial intramuscular dose of atropine is required to achieve atropinisation in a clinically useful time frame.

At present dosing approaches are limited by available marketed pharmaceutical formulations.

As the dose required in individual children may be unpredictable, there is a need for pragmatism in dosing schedules. We propose initial doses should be based on an equivalent of a single 6 mg atropine dose in an adult.

Calculating accurate doses depending on the age and weight of children is a major difficulty for emergency responders.

On consideration of available kinetic data, clinical experience with atropine in this and other scenarios, and other published advice from international organisations regarding recommended

doses, we would propose a pragmatic approach of 1 mg atropine for a child weighing 10 kg or less (age ⩽1 year); 2 mg for a child weighing 10–20 kg (age 1–5 years); 4 mg for a child weighing 20–40 kg (age 5–10 years) and 6 mg for a child weighing 40 kg or more (age ⩾10 years) as appropriate. As no current autoinjector in the UK contains 1 mg atropine combined with an oxime, the use of a 2 mg atropine/600 mg pralidoxime autoinjector (mark 1 kit) is suggested as a minimum initial dose for all children under 5 years, with larger doses for older children as set out above.

Acknowledgements: The authors would like to thank Dr Kerry Foxall, HPA Chilton, who assisted in the literature search.

Competing interests: None.

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Emerg Med J 2009 26: 690-694
doi: 10.1136/emj.2008.060384