Nerve Agent Attacks on Children: Diagnosis and Management

Joshua S. Rotenberg, MD, MMS, FAAP*, and Jonathan Newmark, MD, FAAN‡

ABSTRACT. Nerve agents (NAs) are the most lethal chemical weapons. We review the pathophysiology and management of NA poisoning of children. NAs cause cholinergic crisis. Children may manifest signs of cholinergic poisoning differently than adults. Children may be less likely to manifest miosis and glandular secretions. They may present with neurologic derangements alone. The goals of treatment should be to limit additional exposure, to provide respiratory support, and to prevent neurologic morbidity. Autoinjectors are optimal delivery vehicles for intramuscular antidotes and are likely to be used in civilian prehospital care. Antidotes include anticholinergics, oximes, and benzodiazepines. Several medications may be available within each class of antidotes. Clinicians will select an antidote based on the status of the individual victim, the accessibility of supportive care, and the availability of the drug. Atropine is well-tolerated and high doses may be required. The oxime pralidoxime chloride has a longer half-life in children. Currently, diazepam is the standard NA anticonvulsant. Midazolam may be the most effective intramuscular anticonvulsant after NA exposure, but, despite its efficacy, it is not an approved agent for seizures. Supportive care and long-term complications are summarized. *Pediatrics* 2003;112:648–658; *chemical warfare agents, terrorism, organophosphorus compounds, sarin, atropine, benzodiazepines, pralidoxime compounds, all children (0–18 years of age).*

ABBREVIATIONS. NA, nerve agent; OP, organophosphorus; WMD, weapons of mass destruction; AChE, acetylcholinesterase; ACh, acetylcholine; CNS, central nervous system; CN, cyanide; NMDA, N-methyl-D-aspartate; FDA, Food and Drug Administration; AI, autoinjector; IM, intramuscular(ly); IV, intravenous(ly); 2-PAM, pralidoxime chloride; CPK, creatine phosphokinase; EEG, electroencephalographic.

> "First, I saw people behaving strangely and so were the animals, acting as if they were struggling. Some were lying on the ground. I saw birds falling off the trees. . . I felt like I was weak, unable to run or fully control my movements. My mouth was full, I could not see properly, but worst of all, I could not breathe normally. I did not know what I was doing and realized that I must be dying. I can not remember any more and I must have lost concience [sic].[1]"

Nerve agents (NAs) are the most lethal chemical weapons. Terrorists have deployed NAs in attacks on unprotected civilians, and terrorists have expressed interest in them.[2] The United States and several of its potential adversaries maintain stockpiles of NAs. Six US military stockpiles of old NA munitions await destruction.[3]

NAs are organophosphorus (OP) anticholinesterase compounds. OPs are ubiquitous as insecticides, in veterinary medicine, and in industry. OP poisoning is commonly reported internationally.[4–6] NAs are more toxic than OP pesticides by orders of magnitude.

Emergency planners may encounter difficulty when planning for pediatric victims of chemical weapons. Many emergency response plans have been largely based on military chemical casualty care doctrine, which has been designed to protect the healthy adult war-fighter on the battlefield. At the same time, some civilian physicians may be unfamiliar with chemical weapons, because they are restricted to military use.[7]

We review the threat of NAs and the management of pediatric victims. There is virtually no primary literature dedicated to the topic. Unfortunately, current events dictate a need for reasonable suggestions for the care of pediatric NA casualties. We have extrapolated from the published literature in diverse medical fields: military medicine, OP pesticide poisonings, epilepsy, disaster medicine, and related animal research. We intend both to guide the individual pediatrician facing a mass casualty scenario and to raise questions for further discussion and study.

HISTORY: MILITARY USE AND TERRORIST THREAT

NAs were first synthesized in Germany in the 1930s as insecticides. Although Nazi Germany weaponized and stockpiled NAs, they were never used in combat. NAs carry a 2-letter nomenclature agreed on by the North Atlantic Treaty Organization. The G series agents were synthesized in prewar Germany, while the V series weapons (eg, VX) were synthesized after World War II. Of all known toxins, only botulinum toxin is more toxic than VX. Still newer agents combine the high lethality of VX with the rapid aging of soman.

During the Iran-Iraq War (1981–1988), Iraq used the NAs tabun and sarin as well as the vesicant sulfur mustard.[8] Some estimate that chemical weapons casualties amounted to ". . . 50 000 mild cases,

From the *Departments of Child and Adolescent Neurology and Pediatrics, Walter Reed Army Medical Center, Washington, DC, Uniformed Services University of the Health Sciences, Bethesda, MD; and the ‡Chemical Casualty Care Division, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland; Department of Neurology, Uniformed Services University of the Health Sciences, Bethesda, Maryland.
Received for publication Sep 17, 2002; accepted May 20, 2003.
The opinions expressed herein are those of the authors and not necessarily those of the Department of the Air Force, the Department of the Army, or the Department of Defense.
Address correspondence to Major (Dr) Joshua Rotenberg, Department of Child and Adolescent Neurology, MCHL-MR, Bldg 2, Rm 1L, 6900 Georgia Ave NW, Walter Reed Army Medical Center, Washington, DC 20307. E-mail: joshua.rotenberg@lackland.af.mil

50 000 moderate to severe cases, and 5000 fatal cases of war gas poisoning. . . 25 000–30 000 of these were civilians."[9] One physician reports that many mild and moderate cases were never counted.[8] NAs are highly lethal when used by the military against civilians. Survivors reported that children were disproportionately affected by the chemical attacks, ". . . virtually all the dead who were seen by journalists were women, children, and old men."[10] To date, no epidemiologic or toxicologic studies have been published.

About half of the terrorist incidents with an identified weapons of mass destruction (WMD) agent have involved chemicals.[11] NAs are attractive weapons to malefactors who wish to be inconspicuous. NAs are generally clear and often odorless liquids at room temperature. Significant doses can be hidden in personal items, and delivery system can be simple. The component chemicals are available for benign chemical syntheses, and the starting materials are easily acquired.[12] The methods for NA synthesis are easily acquired.

A Japanese religious cult, Aum Supreme Truth (Aum Shinrikyo), independently manufactured numerous WMD. After failed attempts to use anthrax and botulinum toxin, the group deployed sarin in 2 attacks.[13] In Matsumoto (1994), 600 people were poisoned, 58 were hospitalized, and 7 died.[14] The ages of the victims ranged from 3 to 86 years. Secondary exposures occurred among first-responders and hospital staff, but the exact number is unknown. One follow-up survey of 52 rescuers identified chronic symptoms in 18 (35%).[15] Their attack on the Tokyo subway (1995) resulted in 5500 people seeking hospital evaluation and 12 deaths. One hospital's emergency department evaluated 640 patients on the day of the attack and admitted 111 of those patients (17%).[16] In the first week after the attack, 1410 additional outpatients presented to this one hospital reporting exposure. The age range in one hospital was 8 to 65 years, including 5 pregnant women. No analysis of the pediatric victims has been published.

Several factors limited the lethality of these attacks, including the terrorists' mismanagement of delivery systems, changes in wind patterns and the use of an impure, 30% dilution of sarin.

TOXICOLOGY OF NERVE AGENTS

As OP compounds, NAs primarily act by inhibiting esterase enzymes. Acetylcholinesterase (AChE) is the most pathophysiologically significant of these enzymes. The NAs bind to AChE, preventing it from hydrolyzing acetylcholine (ACh). Cholinergic crisis erupts when excess neurotransmitter accumulates in the synaptic space and overstimulates both muscarinic and nicotinic receptors. NAs also bind to esterases in the erythrocytes and serum. Although pathophysiologically less important, activities of these enzymes serve as quantifiable proxies of exposure.

Individual NAs range in their lethality. A dermal exposure to 10 mg of VX is lethal in 50% of typical adults (LD_{50}), while 1.7 g of liquid sarin is required for 1 LD_{50}. A vapor's lethality is more difficult to quantify, as the dose varies in proportion to the product of the concentration and the time exposed ($C \times t$). For instance, the lethal dose of sarin in 50% of individuals is 100 mg $\times$ min/m^3 (LCt_{50}). One is effectively exposed to the same dose at a concentration of 100 mg/m^3 for 1 minute or 10 mg/m^3 for 10 minutes. The relationship between concentration and time underscores the need to rapidly evacuate to a vapor-free environment.

A vapor exposure may cause a paroxysmal onset of either full or partial cholinergic crisis (see Table 1). A high dose may directly cause central apnea, loss of consciousness, or seizures. A low vapor dose may cause only local respiratory or gastrointestinal effects, maximal soon after onset. After removal from the vapor, other cholinergic signs should not progress. If cholinergic crisis worsens, one should suspect a concomitant contact with liquid.

A dermal liquid exposure may start with only local diaphoresis and fasciculations. As the agent is absorbed, systemic signs will manifest as long as 18 to 24 hours later. Decontamination prevents absorption of agent but is ineffective against NA that is already absorbed.

Respiratory failure is the primary cause of death in NA-exposed victims. NAs poison the respiratory system at multiple levels by causing central apnea, flaccid neuromuscular paralysis, bronchoconstriction, and profound glandular secretions. At low doses of vapor, individuals experience dyspnea, increased airway secretions and a sense of chest tightness.[17] Clinical experience with occupational exposures has shown that evacuation alone can reverse the pulmonary dimension of this syndrome. At higher concentrations of OP exposure, sudden central apnea causes respiratory failure. Atropine reverses central apnea, relieves bronchoconstriction, and dries secretions. Atropine will not improve neuromuscular function, particularly diaphragmatic function.

Miosis is a hallmark sign of exposure to OP compounds in adults. It can be evident even at low doses of exposure to NA vapor.[18] Miosis does not readily respond to systemic treatment and can persist for weeks after exposure.[19] Eye pain and blurring are also frequent complaints. There is debate about

TABLE 1. NA Toxicology—Summary

- Overstimulation of ACh receptors causes cholinergic crisis.
- Death is primarily attributable to respiratory failure
- Cholinergic crisis—"B-A-G the P-U-D-D-L-E-S"
  - Bronchoconstriction
  - Apnea
  - Graying/dimming of vision
  - Pupillary constriction (miosis)
  - Urination
  - Diaphoresis
  - Defecation
  - Lacrimation
  - Emesis
  - Seizures
- NAs disrupt function of AChE at muscarinic (brain, glands) and nicotinic (neuromuscular junction) receptors.
- Atropine, a muscarinic receptor antagonist, does not reverse nicotinic effects.
- Signs depend on dose and route of exposure (vapor of liquid) as well as the time exposed (vapor).

whether the complaints of dim vision result from miosis, retinal pathology or central nervous system (CNS) dysfunction.[20]

In the CNS, OP compounds have both acute and longer-term effects.[18] The cholinergic system has widespread distribution in the CNS, and it plays primary roles in attention, arousal, and memory. Currently, it is thought that cholinergic receptors in CNS are roughly 90% muscarinic and 10% nicotinic. Classically, it has been theorized that NAs directly inhibit AChE, increasing available excitatory ACh and thus precipitating seizures. Soon after NA exposure (<5 minutes), atropine alone can be an effective anticonvulsant. Anticholinergics lose this effect as both the cholinergic surge as well as the early seizures themselves recruit other neurotransmitter systems. This surge also activates excitotoxic injury numerous cortical and subcortical areas.[21] With atropine, anticonvulsants arrest seizures and prevent secondary CNS damage.

NAs initiate a series of neurotoxic events even without causing seizures. Neuropathology can be observed in animals at subconvulsive doses.[22] OP compounds can directly interact with numerous neurotransmitter receptors, (eg, ACh-nicotinic, ACh-M2, and γ-aminobutyric acid $[GABA]_A$), second messengers, and neuronal structural proteins.[20,23–25]

NAs have a marked effect on the peripheral nervous system where ACh is the dominant neuro transmitter. The distinction between muscarinic and nicotinic receptors is clinically significant. Antimuscarinic antidotes, such as atropine, will not reverse nicotinic effects. At the neuromuscular junction, overstimulation of the nicotinic ACh receptors can cause fasciculations, cramps, weakness, and then paralysis. In addition, nicotinic receptors receive cholinergic input from the preganglionic nerves in the sympathetic nervous system. Cardiovascular effects of NAs vary with individual balances of vagal muscarinic and sympathetic nicotinic effects. One may observe bradycardia or tachycardia and hypertension.

VULNERABILITIES IN CHILDREN

Many physiologic and behavioral characteristics unique to children make them vulnerable to toxic exposures, including NAs. Anecdotal and uncontrolled studies have claimed that children are likely to be the first to manifest symptoms, to develop more severe manifestations and to be hospitalized for other related illnesses.[26–29] Two articles discuss the general vulnerabilities of children to the effects of WMD.[7,30]

A child's smaller mass alone reduces the dose of NA required to cause observable and lethal effects. One source calculated by body weight alone that the LCt_{50} of sarin for a resting infant was 47 mg × min/m^3 while that for a resting adult male was 100 mg × min/m^3.[31] At levels of light activity, the dose decreased to 70 and 33 mg × min/m^3, respectively. This author did not take into account any other physiologic factors. Research on OPs has shown greater vulnerability in immature animals than in adults.[32] One OP was found to have a LD_{10} (dose lethal to 10% of a population) that was approximately one tenth that of an adult when dosed in equivalent mg/kg.[33] Single low does of OP pesticides have been linked to developmental disorders in juvenile mice.[34]

Several factors contribute to respiratory vulnerabilities in children. Because NAs produce copious secretions and bronchospasm, one should anticipate a clinical picture resembling status asthmaticus. Sources of respiratory vulnerability in children that are pathophysiologically important in cholinergic crisis include: smaller airway diameter, anatomic subglottic narrowing, relative nose-breathing, omega-shaped epiglottic structure, relative tongue size, abdominal girth, and less rigid ribs and trachea.

With a higher respiratory rate and minute volumes than an adult, a child will inhale a greater dose of NA at a constant concentration of toxic vapor. Children have more limited endurance of their accessory muscles of breathing, putting them at risk for respiratory failure.

Children have lower reserves of fluid and a cardiovascular system with a limited repertoire of stress responses. Intravascular volume can be quickly compromised by significant loss of fluids from the gastrointestinal tract and from glandular secretions. In younger children, cardiac output is strongly dependent on heart rate, while blood pressure is maintained until an advanced stage of shock.

NAs may be able to access the immature CNS more easily than in adults, as not all functions of the blood-brain barrier develop simultaneously.[35] Infants and children are more seizure-prone than adults. The immature brain varies with regard to neurotransmitter concentrations, actions, receptor subtypes, and receptor density. Infants are the most susceptible to imbalances of excitatory and inhibitory neurotransmitter systems. Clinical and laboratory experiences validate this tendency of the immature brain toward excitability. Pilocarpine, a cholinergic compound used in animal models of seizures, requires a significantly lower dose to induce convulsions in immature animals.[36]

The highest incidence of seizures is observed in the first year of life, and the greatest incidence of status epilepticus occurs in the first 2 years.[37] Among all age groups, those under 4 years with status epilepticus have the highest risk of death (3–4.5 times) in hospital when compared with patients without status epilepticus, even when adjusted for comorbid conditions.[38] Numerous lines of evidence show that prolonged seizures can permanently alter brain development in a way that impairs learning, increases seizure susceptibility, and increases the risk of subsequent neuronal injury.[39] Although refractory status epilepticus is not common, mortality is high (~20%–30%) and few children return to their neurologic baseline even with optimal care.[40]

Once exposed to an OP agent, children have less mature innate metabolic systems for detoxification. Paraoxonase is a naturally occurring triesterase enzyme that detoxifies OP pesticides. Certain genotypes have been associated with a heightened susceptibility to the effects of OPs.[41] By some estimates, paraoxonase levels at birth are about half those of

adults.[42] This may imply that young children are more vulnerable to both OPs and NAs.[43]

Behavioral factors could increase vulnerability. Children vigorously playing outside or who cannot follow protective instructions might receive a higher dose.[29]

CLINICAL PRESENTATION IN CHILDREN

Children exposed to a NA might present with a clinical picture unlike that observed in adults. Children in cholinergic crisis may not necessarily manifest miosis. In a recent series of severe anticholinesterase pesticide poisonings in children aged 5 months to 14 years, miosis was absent in 43%.[44] It is unclear if this observation resulted from the oral route of exposure or from a developmental parasympathetic response.

One series of OP-exposed children presented with isolated CNS effects (stupor, coma) in the absence of peripheral muscarinic effects.[45] The electroencephalographic (EEG) correlate of the victims' stupor is unreported in this study, and it is therefore impossible to discern how many victims experienced nonconvulsive status epilepticus. Only 8% to 22% presented with frank seizures.[44,46] Significant weakness and hypotonia have been observed in 70% to 100% of pediatric victims in all of these series with moderate to severe exposures. Weakness and hypotonia in the absence of glandular secretion or miosis would not fit the typical profile of an adult NA vapor victim.

CLINICAL MANAGEMENT: OVERVIEW

Pediatricians should be familiar with the response to a chemical weapons attack although it is outside the scope of their usual practice. Municipalities have developed detailed and coordinated regional plans for a response to chemical terror. Physicians will play essential roles as clinicians, leaders, and educators in a real-world event.

The general priorities after a NA attack are: evacuate the toxic zone, triage victims, decontaminate, resuscitate victims while initiating antidotal treatment, and secure definitive treatment. This is not a rigid sequence. In cases of severe poisoning antidotal treatment must start before full decontamination can occur.

CLINICAL MANAGEMENT: DIFFERENTIAL DIAGNOSIS

A chemical exposure should enter the differential diagnosis in all mass casualty events manifesting with respiratory and neurologic symptoms. Carbon monoxide, hydrogen sulfide, certain metal exposures, and xylene can cause an acute encephalopathy and convulsions. Any gas at sufficient concentration can cause narcotic effects. Typically, however, these syndromes develop over days of progressive impairment of mental status and/or have a clear antecedent (ie, industrial exposure, use of glues). Until a chemical is identified, decontamination and treatment should be initiated based on clinical suspicion.

Only 2 classes of chemical warfare agents cause the acute onset of respiratory symptoms and neurologic dysfunction: NA and cyanide (CN). It is most important to distinguish these agents acutely, as the antidotal regimen differs. CN is a relatively ineffective poison for outdoor use, but its indoor lethality makes it an attractive weapon of terror. By obstructing aerobic metabolism, CN causes neurologic and cardiac dysfunction, including central respiratory arrest and myocardial depression. CN victims present without miosis and usually without cyanosis. Although seizures may be present, neuromuscular symptoms are absent. Like NA, CN can cause hypersalivation, nausea, and vomiting.

In an unknown exposure with individuals complaining of shortness of breath, riot control agents (eg, pepper spray) may enter the differential diagnosis. These aerosolized solids cause a rapid onset of symptoms with fairly low exposures. Pulmonary agents (chlorine or phosgene) or toxins (eg, botulinum toxins) can cause neurologic and respiratory symptoms. The patient's sensorium should be intact in the initial stages, as CNS dysfunction is not a primary manifestation of exposure but a secondary effect of a physiologic derangement (eg, hypoxia). The agents present more gradually than do NAs.

LABORATORY TESTING

When an acute NA exposure is suspected, treatment cannot await laboratory confirmation. Measurements of cholinesterase levels will not be helpful in establishing a diagnosis acutely, especially without a baseline. There is a wide variation in the population for AChE levels by ethnic group, age and reproductive status. Red blood cell (RBC) AChE levels are lower in infants (50%–70%) than normal nonpregnant adults.[47] In pregnancy, RBC levels can be elevated and serum AChE levels can be reduced compared with nonpregnant controls. Although RBC cholinesterase levels correlate with brain ChE more closely in younger animals than older ones, the delay until reporting results still limits its utility for an acute diagnosis in children. Measurements of serum or RBC AChE may still be useful for confirming the diagnosis, for monitoring recovery, or for forensic study. Arterial blood gas can provide clues for CN exposure including metabolic acidosis with both a high anion gap and high lactate concentrations.

CLINICAL MANAGEMENT: TRIAGE

The key to management of any mass casualty scenario is rapid and efficient triage, because delay in treatment will increase mortality and morbidity. Several military and civilian models are available.[48,49] Criteria for assigning specific triage levels after a NA attack and corresponding guidelines for antidotal treatment are listed in Table 2.

There are compelling medical and behavioral reasons to establish pediatric-specific zones at the scene of a chemical attack.[50] Clinical activities that are normally performed by rote on adults can be transformed into nonautomatic processes (eg, weight estimation, equipment selection, and calculation of ventilatory parameters, recall/referencing doses of antidotes, and the calculation of drug doses).[51] Inefficiencies will contribute to increases in the risk of intensive care unit admission, requirements for ven-

TABLE 2. Pediatric NAs: Triage and Dosing Card

Symptoms	Triage Level: Disposition	Anticholinergics	2-PAM	Benzodiazepines Monitor Respiratory Status and Blood Pressure
Asymptomatic	Delayed: Observe	None	None	None
Constricted pupils or mild rhinorrhea	Delayed: Admit or observe	None	None	None

Constricted pupils and any other symptom of cholinergic crisis	Immediate: Admit	Atropine—0.05 mg/kg IV/IM/IO to maximum 4 mg
		• Repeat as needed every 5–10 min until pulmonary resistance improves or secretions resolve
		• Correct hypoxia asap
		• Alternatives
		  • Nervous system and peripheral effects—consider scopolamine
		  • Peripheral effects only—glycopyrrolate
			2-PAM 25→50 mg/kg IV/IM to 2000 mg maximum/h
			• Repeat every 1 h prn.
			• Watch for:
			Muscle regidity
			Laryngospasm,
			Tachycardia
			Hypertension
				Neurologic effects? Rapid progression?
				1. Midazolam IM, IV
				  • 0.15–0.2 mg/kg
				  • Repeat as necessary or start continuous IV drip
				  • Less likely to cause apnea by IM route
				2. Diazepam (PR, IV—see below), or Lorazepam (IV) 0.05 to 0.1 mg/kg
				No IV or IM available? Consider: midazolam—sublingual, intranasal—0.2 mg/kg or diazepam pr or lorazepam pr

Apnea, convulsions, cardiopulmonary arrest Or rapid progression	Immediate: Admit intensive care status	Atropine 0.05 to 0.10 mg/kg IV/IM/IO
		• Repeat every 5→10 min as above—no maximum
		• Endotracheal tube: ↑ dose by 2–3 x,
		  • Mix with 3–5 mL normal saline and introduce via suction catheter, flush 3–5 mL NS
			2-PAM 25→50 mg/kg IV or IM as above to 2000 mg maximum/h	1. Midazolam as above
				2. Diazepam IV
				  • 30 d to 5 y—0.05–0.3 mg/kg IV
				  • Maximum of 5 mg/dose.
				  • 5 y and older—0.05–0.3 mg/kg IV
				  • Maximum of 10 mg/dose.
				  • Repeat every 15–30 min prn
				3. Lorazepam IV, IM

AI		Atropine: −2 mg for 40 kg+ −1 mg for 20 kg+ −0.5 mg for 10 kg+ (0.05 mg/kg/dose)	2-PAM: 600 mg for 12 kg+ (50 mg/kg/dose)	Diazepam −10 mg fo 30 kg+ (0.3 mg/kg/dose)

IO indicates intraosseous; PR, per rectum; NS, normal saline.
• Remember: airway, breathing, circulation, decontamination/drugs.
• Consider: oxygen, bronchodilators, NG tube/drainage, ophthalmic analgesia, mydriatics, temperature control.
• Prolonged impairment of consciousness→EEG to rule out nonconvulsive status epilepticus, imaging.

tilatory support, and overall morbidity. A recent review of an Israeli hospital's response plan included a pediatric zone. Their plan allowed specialization of care, concentration of resources, and attention to behavioral issues.[52] Few similar plans exist in the United States.

No studies have been performed to establish optimal methods for evaluating and decontaminating groups including children. A review of decontamination procedures lies outside the scope of this article.

CLINICAL MANAGEMENT: TREATMENT AND ANTIDOTES

The pillars of therapy for any NA casualty include: intensive respiratory care, antidotal therapy, treatment of complications and monitoring, and care for long-term sequelae.

RESPIRATORY SUPPORT

Respiratory failure and hypoxia are the main causes of acute morbidity and mortality in OP poisoning. OP pesticide poisoning may require mechanical ventilation for days.[53] Because NAs are less fat-soluble than the OP pesticides, victims of NA exposure are less likely to require extended ventilatory support. At one hospital in Tokyo, after the 1995 subway attack, 4 of 640 (0.6%) victims required mechanical ventilation and 3 of 4 survived without sequelae.[54] Except for 1 fatality, all were extubated in 2 days.

In a severe exposure, inadequate respiratory effort might be followed by central apnea, which is resistant to antidotes. When considering mouth-to-mouth resuscitation, one should note that 10% of inhaled NA is expired. To prevent secondary contamination of the ventilatory apparatus, one should introduce a filter between the patient's tracheal tube and the ventilator tubing. A bag-valve-mask with an in-line filter is commercially available.

Airway resistance will be high (up to 50–70 cm H_2O) because of bronchoconstriction and copious secretions.[17] In the absence of secretions, atropine should be administered until resistance diminishes and adequate ventilation is achieved. Nebulized β-agonists should be administered to treat bronchoconstriction. Emesis is frequently observed in cholinergic crisis, and gastric contents should be drained.

Ketamine (an antagonist of glutamatergic N-methyl-D-aspartate [NMDA] receptors and a bronchodilator) should be used with caution in a NA casualty. In animal OP exposures, central apnea quickly ensued when other NMDA receptor antagonists were administered before atropine.[55] Atropine pretreatment prevented this effect.

CLINICAL MANAGEMENT: ANTIDOTES

Several reviews address the antidotal therapy of NA in adults.[18,19,56] In pediatrics, most NA treatments are considered off-label uses. Only 1 antidote is indicated for OP poisoning (pralidoxime chloride), and only 2 benzodiazepines with parenteral preparations (diazepam and lorazepam) are approved for seizures. Our recommendations for dosing (see Table 2) are derived from the best synthesis of the adult and pediatric literature. No safety data on immature animals poisoned with NAs has been derived. At a time of crisis, pediatricians will have to use their clinical judgment to manage individuals optimally.

Severely poisoned victims require treatment as quickly as possible. Stabilization and antidotal treatment should begin even before decontamination in the most emergent group of victims.

Civilian physicians are likely to see military-style Mark 1 kits in a NA event. Municipalities are purchasing these Food and Drug Administration [FDA]-approved autoinjectors (AIs) for emergency responders. The current kits contain 2 AIs: one with 2 mg of atropine and another with 600 mg of pralidoxime chloride. In 2001, the FDA approved a combined AI containing both agents at the above doses.

AIs are superior intramuscular (IM) delivery vehicles for antidotes when compared with the needle and syringe method. Instead of creating a small pool of medication, they discharge the medication as the needle pierces the tissues. Activated AIs deploy in all-or-nothing fashion and can achieve peak serum concentrations of atropine in <5 minutes. In contrast, when 0.02 mg/kg of atropine was intramuscularly injected in children, maximal effect was not reached for 25 minutes; far too late to treat NA exposure.[57]

ANTICHOLINERGICS: ATROPINE

Atropine, a competitive antagonist of ACh muscarinic receptors, is the primary antidote after a NA exposure. Atropine reverses the peripheral muscarinic symptoms (eg, secretions and airway resistance) and arrests the early phase of convulsions when given within 5 minutes of exposure.[58]

The dose of atropine recommended for the treatment of symptomatic bradycardia in children (usually 0.02 mg/kg) is likely to be inadequate. Forty-seven adults with OP poisoning required an average of 79.1 mg (range: 16.2–142 mg) of atropine over 1 to 5 days of hospitalization.[53] During the Iran-Iraq war, 1 Iranian physician reports using between 20 and 200 mg of atropine for severely affected soldiers.[8]

The experience of Israeli children who were accidentally atropinized during the Gulf War should reassure the practitioner about the relative safety of atropine in children. Pediatric atropine AIs were distributed in 3 sizes (0.5 mg, 1 mg, and 2 mg), and the activation force was 1.4 to 1.8 kg. During the war, 240 children presented to Israeli emergency departments after receiving accidental injections. The doses ranged between 0.01 and 0.17 mg/kg. The main untoward effects were dilated pupils, tachycardia, dry mucous membranes, flushed skin, temperature >37.8 degrees, and neurologic abnormalities. Doses up to 0.045 mg/kg did not produce signs of atropinization. There were no fatalities or life-threatening dysrhythmias. Only 2% of the children were admitted for 24 hours of observation for sinus tachycardia and/or agitation.[59]

An atropine dose of at least 0.05 mg/kg IM or intravenously (IV) is suggested for a child with moderate or severe manifestations of NA exposure (see Table 2). Atropine AIs (2 mg) can be safely be used in

children weighing 40 kg (0.05 mg/kg) or more. In a clear cholinergic crisis, a higher dose (0.1 mg/kg) should be considered and thus a 20-kg child may receive a 2-mg atropine AI. Using a needle and syringe, atropine can be administered by the IV, intraosseus, IM, rectal, oral, or endotracheal routes.

Some sources advocate tachycardia or drying of secretions as an end-point for atropinization. Children, however, are less likely to develop tachyarrhythmias and may never produce excessive secretions. Although these effects are significant, the focus should remain on the patient's respiratory status. Atropine should be administered until bronchospasm improves. When administering assisted ventilation, resistance will palpably improve.

Atropine has significant untoward effects and limitations, and individual tolerance is unpredictable. Small doses will commonly cause an increase in heart rate, dry mouth, dry skin, mydriasis, and dysfunction of accommodation. Near vision may be impaired for 24 hours. Even small doses prevent sweating, and exacerbate heat stress. Atropine also causes relaxation of the lower esophageal sphincter, hyperthermia, and paralytic ileus in adults.

Although atropine has been the anticholinergic agent of choice for NA exposure many years, any anticholinergic agent will have antidotal properties. In certain clinical situations, such as a limitation of supplies or atropine allergy, one might use other anticholinergic agents such as glycopyrrolate and scopolamine.[60] Glycopyrrolate is a reasonable choice for mildly affected victims as an anti-sialogogue or as a peripheral parasympatholytic. Glycopyrrolate does not cross the blood-brain barrier and would thus be ineffective for central effects. Scopolamine is an effective NA antidote, but unlike atropine or glycopyrrolate, it causes profound CNS effects, including sedation. In animal models, scopolamine administered 40 minutes after exposure was a more effective antidote than atropine.[58]

OXIMES

Oximes are used as adjunctive antidotes for OP poisoning, and pralidoxime chloride (2-PAM) is the agent of choice in the United States. Oximes hydrolytically cleave the OP from AchE, restoring enzymatic function.

After a NA binds to AChE, a reaction known as aging occurs; a chemical substituent is lost, bonding the NA-AChE complex irreversibly. The complex then resists reactivation by oxime antidotes. NAs vary in their rates of aging, with soman, the fastest, taking only minutes. A 5% to 10% therapeutic benefit may still be realized by oxime therapy in soman exposure.[61]

A typical dose of 2-PAM in children exposed to organophosphates is 20 to 50 mg/kg to a maximum of 2000 mg/h.[62] From a Mark 1 autoinjector kit, one 600-mg dose of 2-PAM might be used in a child over 12 kg, but before administration one should consider the length of the needle (~1 inch) in choosing a site of injection.

Repeated doses may be necessary. In 1 series of OP poisonings, where the doses ranged form 25 to 50 mg/kg, 1 child received 26 doses of 25 mg/kg over days of treatment.[46] A series of OP poisoning in children outlined the pharmacokinetics of a continuous infusion of 2-PAM in children.[63] Eleven subjects received loading doses of 15 to 50 mg/kg IV and were started on a maintenance drip of 10 to 20 mg/kg/hour. There were no untoward effects in this series. Of note, the half-life in this series of children was noted to be approximately twice that observed in adults.[64] Doses might not need to be repeated as frequently as the 1 hour recommended in adults.

Common untoward effects include dizziness, transient diplopia, and blurred vision. One should adjust the dose in individuals with renal insufficiency, because 2-PAM is excreted almost entirely unchanged by the kidneys. Rapid IV administration can cause laryngospasm and rigidity. Hypertension is the most serious untoward effect at higher doses, but mild electrocardiographic changes can be observed at somewhat lower doses.

Benzodiazepines

Seizures should be prevented and treated when they occur. One should assume a potentially neurotoxic exposure of NA if >1 organ is involved, if consciousness is impaired, or if the patient has diffuse muscle twitching.

Administration of anticonvulsants thwarts status epilepticus and prevents secondary neurologic injury. Benzodiazepines are the only reliably effective agents in NA-induced seizures. Phenobarbital has been noted to have a moderate effect at anesthetic doses (40 mg/kg), but it should not be considered without adequate support. The anticonvulsant effect of benzodiazepines is enhanced by atropine. Currently, diazepam and lorazepam are the only benzodiazepines with IV preparations approved by the FDA for the treatment of seizures of any type.

Diazepam is highly lipophilic. It enters the brain quickly but also quickly redistributes. IV diazepam has an anticonvulsant effect within 3 minutes, but after 20 minutes, blood concentration decreases by 34% to 50%.[65] As a result, seizures may recur. Although IM dosing results in erratic absorption, IV access will not be immediately available to the average war-fighter on a battlefield. Consequently, IM injection of diazepam is advocated by current military doctrine despite its being contraindicated in most civilian settings. Because of the current regulatory status and storage requirements, the Department of Defense deploys an AI with 10 mg of diazepam. Diazepam may not be the optimal medication for this purpose and its use may present risks in pediatrics.

A rectal gel preparation of diazepam has proven effective and safe in the management of status epilepticus. The incidence of diarrhea in OP poisonings has been observed to be low (9%), and hence this diazepam preparation may be considered.[44] No human or animal data are available for rectally administered diazepam in a NA exposure.

Like diazepam, lorazepam manifests anticonvulsant activity within minutes of absorption. Lorazepam has several advantages over diazepam. Loraz-

epam's antiepileptic properties can persist for hours when it is eliminated (somewhat more quickly than diazepam). In adults, the elimination half-life is 10 to 15 hours, and in children, its effects may persist for 48 hours. Diazepam has a markedly prolonged elimination half-life in infants (31–75 hours).[66] Some have reported that lorazepam has a better safety profile in children. In a study of children in status epilepticus, 27% of the group receiving lorazepam required intubation, when 73% of the diazepam group required intubation.[67] In animal models, however, lorazepam is less effective than diazepam against NA-induced convulsions. Like diazepam, lorazepam is not an optimal choice when IV access is not available as it has variable absorption after IM administration.

Midazolam, in contrast, is notable for its water solubility, short-onset of action, short half-life, and lack of active metabolites. When injected IM, the physiologic pH induces a shift toward lipid solubility that in turn facilitates passage through the blood-brain barrier. Midazolam has been formulated for a number of routes of administration: oral, IV, IM, intranasal, and sublingual. It appears to be the optimal choice for IM administration during status epilepticus. A prospective, randomized study comparing the anticonvulsant properties of IM midazolam and IV diazepam showed that there was approximately a 4-minute difference in both the times for drug administration and seizure cessation in favor of IM midazolam.[68]

IM midazolam is more efficacious in arresting NA-induced seizures in animals than other benzodiazepines.[69] In the coming years, Israel will deploy midazolam as their nation's first-line NA anticonvulsant. Although many experts in chemical defense increasingly favor midazolam, the pediatrician should be cautioned that the elimination half-life in children is as short as 1.4 to 4.0 hours.[70]

A benzodiazepine should be considered even when there is a suspicion of seizures because nonconvulsive status is common in children and because seizures can be subtle in infants. One clinical series showed that 79% of EEG seizures in infants had no observable clinical manifestations.[71] In an unconscious individual in a mass casualty scenario, it may be even more difficult to diagnose nonconvulsive status epilepticus. If consciousness remains impaired for a prolonged period, EEG should be used to rule out nonconvulsive status epilepticus. Other traumatic causes of impaired consciousness should be considered and acute imaging may be warranted.

CLINICAL MANAGEMENT: CARE OF ACUTE COMPLICATIONS

A recent series noted several complications of OP poisoning: aspiration of gastric contents, excessive secretions, pneumonia, and septicemia.[72] In the sarin attack on Matsumoto, Japan, the critically ill were noted to have hyperglycemia, hypokalemia, and/or hypolipidemia. An increased level of creatine phosphokinase (CPK) was noted in >10% of victims. Neurologically, 22% had headache, 12% had malaise, 6% had dysesthesias, and ~1% had EEG abnormalities. Low-grade fever and leukocytosis were noted in 6% and 9%, respectively. Increased CPK (10%) and leukocytosis (60%) were noted in the 111 hospitalized victims at one hospital in Tokyo.[73]

Cardiac manifestations of OP exposure evolve in 3 phases of variable length. First, there is a brief (minutes) nicotinic phase with hypertension and even tachyarrhythmias.[74] Second, a phase of profound parasympathetic outflow evolves with bradycardia and hypotension. A final phase starts hours to days after exposure with QT prolongation and a tendency toward malignant dysrhythmias. This final phase can persist after other acute cholinergic effects have subsided.[75] In 1 series of serious OP poisonings, 42% manifested cardiac arrhythmias with torsades de pointes in 37%[76] Cardiac arrhythmias in pediatric OP poisonings can portend a grave outcome.[44]

NA exposure may cause hypothermia, but atropine can cause hyperthermia. Either extreme of temperature can worsen outcomes.

One should choose medications to aid in treatment goals and monitor for untoward effects of antidotes and interactions.[77] Use of local or spinal anesthesia will obviate risks of general anesthesia. If general anesthesia is required, volatile anesthetics may be beneficial because of their bronchodilating effects. Depolarizing muscle relaxants might cause unexpected effects with NAs, and other cholinergic agents and require careful monitoring. One short-acting opioid, remifentanyl, could theoretically have a prolonged duration of action after a NA exposure. Remifentanyl is partially metabolized by the hydrolytic action of an esterase, inhibited by NAs.

Urinary retention is a common untoward effect of anticholinergic drugs. Catheterization may be necessary.

Caution should guide advice on human milk feedings after exposure to NAs. NAs, in general, are not highly lipophilic. Although one might not expect significant storage of NAs in adipose tissue, a small dermal exposure may take hours to manifest. Nursing mothers should pump and discard breast milk until a determination of safety can be made. Given the short half-lives of liquid NAs, this interval is likely to be short. No published data on this topic exists.

CLINICAL MANAGEMENT: LONG-TERM EFFECTS

The full spectrum of OP-induced illness can be divided into 3 phases: 1) acute cholinergic crisis, 2) an intermediate syndrome, and 3) delayed effects. There is no literature on the long-term effects of NA poisoning in children, and thus we must extrapolate from the adult literature.

After significant NA exposure, neuropsychiatric and medical sequelae can linger. In a survey 3 weeks after the Tokyo sarin attack, >40% of victims still complained of cough, dyspnea, rhinorrhea, dark vision, and headache.[78] Sarin-exposed victims, when compared with unexposed victims at 1 and 3 years after the Matsumoto attack, had significantly different complaints. The severity of their fatigue, asthenia, shoulder stiffness, insomnia, slight fever, narrowing of the visual field, blurred vision, and asthenopia was positively associated with the grades

of exposure.[79] One individual exposed to soman in the workplace manifested depressed mood, withdrawal, antisocial thoughts, sleep disturbance as well as in impairment of the serial 7s.[18] Scopolamine provided some transient relief. Another 52-year-old individual exposed to sarin still experienced significant fatigability, dyspnea on exertion, restlessness, poorly localized pains, anxiety, and crying spells up to 4 months after exposure. A chronic decline in memory has been observed in first-responders exposed to sarin. When tested 3 years after the incident, backwards digit span was reduced in a dose-dependent manner.[80]

After exposure to sarin, EEG abnormalities can persist for more than 1 year.[81,82] Reduced performance on neurobehavioral tests after exposure has been described.[83–85] Other neurophysiologic changes have been noted, including abnormal evoked potential latencies (P300 and VEP-P100), and vestibulocerebellar damage.[86,87] NA exposure may be neurotoxic even in the absence of seizures. OP pesticides at low, subconvulsive doses have been linked to developmental neurotoxicity by a pathophysiology that is independent of AChE inhibition.[88]

The intermediate neuromuscular syndrome observed after OP poisoning has not been documented after NA exposure. There has been a single case report of NAs causing OP-induced delayed neuropathy.[89]

Although little evidence supports a role for NAs in mutagenicity or carcinogenicity, OPs have been shown to be teratogenic in animals after a first-trimester exposure.[78] One study of the victims of the Tokyo subway attack found a significantly higher rate of sister chromatid exchanges in lymphocytes of those exposed to sarin.[90] If validated in future studies, such genetic aberrations may have utility as an objective marker of exposure.

FUTURE DIRECTIONS

After a chemical attack, physicians of all specialties in any nearby hospital will treat victims of all ages. To prepare realistically for a WMD event, policy makers and planners should include pediatric aspects of care. Mass-casualty exercises should include pediatric vignettes that create realistic scenarios. Simulated victims should present at all ages, ranges of mobility, and with complicating medical problems. Hospitals and hazardous materials response units should maintain a stockpile of pediatric medical equipment. Antidote AIs in pediatric doses may be useful for first-responders to rapidly treat severely affected children. Basic research on countermeasures for WMD should include pediatric-specific protocols. The optimal care of children will enhance overall efficiency and limit morbidity and mortality among all victims.

ACKNOWLEDGMENTS

We would like to thank the following individuals for their support and contributions: Dr Michael Mitchell, Dr Phil Rogers, Dr Beverly Maliner, Dr Thomas Burklow, Dr Clifton Yu, Dr James Madsen, and Leah Pishnov Rotenberg.

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CREDIBILITY OF SUBGROUP ANALYSES

"It is essential that potential subgroup analyses are specified before the commencement of a study to guard against data 'dredging' or 'trawling.' Applying many different statistical tests to the same date (eg, on subgroups or different outcomes) has the effect of greatly increasing the chance that at least 1 of these comparisons will be declared statistically significant even if there is no real difference. This practice is often termed data dredging. However, simply specifying a subgroup analysis in advance does not necessarily add scientific legitimacy to the interpretation. A number of strategies exist to ensure the credibility of subgroup analyses, and a checklist proposed by Simes (personal communication) suggests that the following criteria should be satisfied.

- That there is a *biological rationale* for considering the subgroup separately from the rest of the patients in the study.
- That there is *prior evidence* or *belief* that a differential treatment effect in a subgroup is plausible.
- That there is statistical evidence (ie, a *significant interaction*) of a difference in the effect of treatment for the subgroup in question compared with the other patients.
- That there is *independent confirmation* from other factors in the study of the possible differential treatment effect in the subgroup."

Gebski VJ, Keech AC. Statistical methods in clinical trials. *Med J Aust.* 2003;178:182–184

Submitted by Student

Nerve Agent Attacks on Children: Diagnosis and Management

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Pediatrics 2003;112;648
DOI: 10.1542/peds.112.3.648

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