A review of nerve agent exposure for the critical care physician*

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Nerve agents are discussed. The article discusses their properties, routes of exposure, toxicodynamics, targets of toxicity, and treatment. It is concluded that a focused organized approach to the treatment of nerve agents is key to its successful management. **(Crit Care Med 2002; 30:2346–2354)**

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Nerve agents were [1]developed in Germany during the 1930s as potential pesticides. The agents are traditionally divided into two classes, the G and V agents (1) (Table 1). The G agents were first synthesized in Germany in 1936 by a group of chemists at IG Frbenindustrie. The V agents were first synthesized in the United Kingdom in 1952. The G agents are typified by the compounds known as tabun (GA), sarin (GB), and soman (GD). Only one V compound has been produced in large quantities, VX (2). The U.S. Chemical Weapons Program no longer produces these; however, U.S. stockpiles of sarin and VX remain. These U.S. stockpiles are currently being incinerated and all U.S. stockpiles are scheduled to be destroyed by 2004 (3).

In spite of the United States destroying its nerve agent stockpiles, synthesis and production of nerve agents are well within the capabilities of a good organic chemist who has access to the necessary raw materials and equipment. The nerve agents' formula and synthetic methods are relatively easily obtained from public information sources, including the Internet. For example, Iraqi military scientists used a U.S. patent that was declassified in 1975 to make VX from a precursor compound, EMPTA (O-ethyl-methyl-phosphonothioic acid). Making EMPTA from phosphorous acid was the only difficult step. Thereafter, EMPTA was mixed with room temperature water and another reagent. Then the nerve agent was extracted (4).

Properties

The properties of nerve agents are summarized in Table 2. The nerve agents are esters of phosphoric acid, known as organophosphates. Their general structure is shown in Figure 1.

An organophosphate's rate of reactivity with acetylcholinesterase and its degree of toxicity depend on which compounds are substituted for the X and two R substituents. Extreme toxicity results when strongly electronegative groups such as the halides (e.g., chlorine, fluorine), cyanide, or thiocyanate are present (4). Sarin has the X substituent for thiocyanate (5). The formula of sarin is shown in Figure 2. The V agents are sulfur-containing organophosphates.

At normal temperatures, the nerve agents are liquids. Melting points range from −42°C (soman) to −39°C (VX) (6). Thickening agents, such as acrylates, can be added to some nerve agents. This alters some of the physical properties of the resultant mixture, thus increasing its persistency in the environment.

Sarin is mixable with water (capable of mixing in any ratio without separating into two phases) and hydrolyzed by water to produce a relatively nontoxic product resulting from removal of fluorine. Soman and tabun are moderately water soluble but readily soluble in organic solvents. Tabun is also hydrolyzed by water. VX is only slightly water soluble at room temperature but is miscible in cold water and organic solvents (6).

The G agents are slowly hydrolyzed at neutral and acidic pHs but are rapidly hydrolyzed at alkaline pHs. This alkaline hydrolysis is exploited by decontaminating with alkaline, dilute, household bleach solutions (0.5% sodium hypochlorite). The half-life of sarin in water, with a pH of 7, is 5.4 hrs, vs. a half-life of 15 mins at a pH of 9.0.

The vapor density of a substance is the density of its vapor relative to the density of air at the same temperature and pressure. Because the vapor density is a ratio, it has no units of measurement. Air is assigned a vapor density of 1. Substances with vapor densities greater than one are heavier than air and tend to sink, if undisturbed, for example, by wind. Substances with vapor densities less than one are lighter than air and tend to rise. The vapor densities of all the nerve agents are >1; therefore, their vapors tend to stay lower to the ground and collect in low spots.

Although the vapor pressures of the nerve agents are not high, they are significant. Sarin is most volatile, with a vapor pressure of 2.9 mm Hg at 77°F (Table 3). The most volatile agent, sarin, has a vapor pressure that is >4,000 times that of the least volatile agent, VX (7).

Water, by comparison, is more volatile, with a vapor pressure of 23.8 mm Hg at 77°F. Most importantly, the volatility of the nerve agents (vapor concentration in mg/m^3) exceeds their recommended control limits for workers exposed to these agents at U.S. Department of Defense facilities (Table 3).

The volatility of the nerve agents and their rates of vaporization are key physical properties that are responsible for the greatest hazard from these agents (Table 3). Primary vaporization of nerve agents can occur from the heat of an explosive device or from the vaporization of droplets that have been dispersed (aerosolized) by a

***See also p. 2397.**

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Table 1. Names, numbers, and sources of exposure for nerve agents

Common Name	Synonym	CAS No.	Sources of Exposure
Sarin	GB	107-44-8	U.S. and other military chemical weapons depots; illicit manufacturing by terrorists
Soman	GD	96-64-0	Illicit manufacturing by terrorists
Tabun	GA	77-81-6	Illicit manufacturing by terrorists
VX	None	50782-69-9	U.S. and other military chemical weapons depots; illicit manufacturing by terrorists

Adapted from Reference 38.
CAS, Chemical Abstract Service.

Table 2. Chemical properties of nerve agents

Chemical	State	Color	Odor/Irritation	Water Solubility	Boiling Point (°F)	Molecular Weight	Flash Point (°F)
Sarin (GB)	Liquid	Colorless	Odorless	Miscible	297	140.1	NR
Soman (GD)	Liquid	Colorless	Fruity	2.1%	333	182.2	250
Tabun (GA)	Liquid	Colorless to brown	Fruity, like bitter almonds	7.2%	464	162.1	172
VX	Liquid	Colorless to straw	Odorless	Miscible if <49°F	568	267.4	318

NR, not reported.
Adapted from Reference 38.
Unless noted, properties are determined at 68°F and an atmospheric pressure of 760 mm Hg (1 atm).

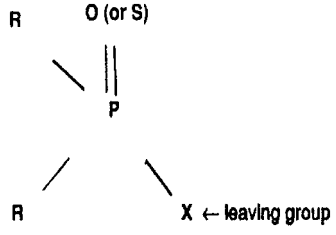

Figure 1. Organophosphate structure.

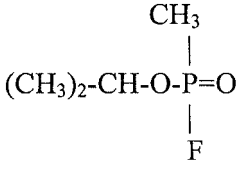

Figure 2. Structure of sarin (GB).

sprayer (7). Secondary vaporization can occur from the ground or other surfaces that have been coated with the liquid or droplets (7). The persistence of a nerve agent is inversely related to its volatility; for example, VX is the least volatile but the most environmentally persistent nerve agent (Table 3).

Routes of Exposure

Inhalation. The three G agents, GA (tabun), GB (sarin), and GD (soman), are volatile liquids at normal ambient temperatures. As can be seen in Table 3, the G agents are significantly more volatile than VX. Consequently, the most likely route of exposure with the G agents is inhalation. Inhalation of VX can occur but is much less likely because of its physical property of low vapor pressure.

Absorption of a nerve agent by inhalation occurs within seconds. However, several factors influence the inhaled dose of vaporized (gaseous) nerve agents. For comparative purposes, the concentration-time function (C*t*) is used to describe the amount of a nerve gas to which a victim is exposed. This term, expressed as C*t*, is equal to the concentration in the air (C), in mg/m^3, times the exposure time (*t*), in minutes. The LCt_{50} is the C*t* that kills 50% of exposed victims. ICt_{50} is the C*t* that incapacitates 50% of the exposed victims. MCt_{50} is the C*t* that produces miosis (pinpoint pupils) in 50% of exposed victims. Table 4 compares these various C*t* values in mg·min/m^3.

Note the very small exposure concentration-times to produce miosis. Also note the small differences between the LCt_{50} and ICt_{50} values. This means only a slight increase in either the time of exposure or the concentration can result in a potentially lethal exposure, rather than an incapacitating exposure.

Skin and Mucous Membranes. All the nerve agents can be absorbed through the skin. However, the more volatile the agent, the larger the topical dose required to produce toxicity. Tabun and sarin generally evaporate before skin penetration can occur. In one study, 25–550 mg of liquid sarin was applied to the forearms of 11 subjects (8). The liquid evaporated from their glabrous skin (skin relatively free from hair) in 1.5–6 mins. Two subjects had transient diarrhea. Sweating continued at the application sites for as long as 34 days. Similar studies have been conducted for tabun, with similar outcomes. Skin exposure to tabun vapors (2.5–5 times the LCt_{50}), either by limbs in chambers or by whole-body exposures with respiratory protection, produced no signs or symptoms of tabun toxicity.

VX is a persistent agent and is well absorbed through the skin after minimal contact time (8). The dermal LD_{50} (the dose applied to the skin required to kill 50% of the victims exposed) for contact with liquid VX, for a 70-kg adult human, is only approximately 6 mg (9–12). In comparison, the dermal LD_{50} for contact with liquid tabun, sarin, and soman is approximately 1610 mg, 1960 mg, and 1260 mg, respectively (4, 9–12).

Clothing that has been sprayed with a nerve agent either can offer a protective barrier that prevents skin contact or can promote continued absorption when wetted sufficiently and allowed to remain in contact with the skin. In a small study of three military officers, 200 mg of VX (20 times the LD_{50}) was sprayed on an outer layer of battle dress serge over flannel and was allowed to remain for 8 hrs (9). About 85% was recovered from the serge and 5% from the flannel. It was suggested that the other 10% vaporized. The sub-

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Table 3. Vapor data and environment persistence of the nerve agents

Name	Synonym	Vapor Density (Relative to air Equal to 1)	Vapor Pressure (mm Hg)	Volatility (mg/m at 77°F)	Recommended Control limit (mg/m at 68°F)	Environmental Persistence
Sarin	GB	4.9	2.9 at 77°F	22,000	0.0001	No
Soman	GD	6.3	0.4 at 77°F	3,900	NR	No
Tabun	GA	5.6	0.04 at 68°F	610	0.0001	No
VX	None	9.2	0.007 at 68°F	10.5	0.00001	Yes

NR, not reported.
Adapted from References 5 and 7.

Table 4. Human lethal, incapacitating, and miosis concentration-time products

Nerve Agent	LCt_{50} (Human)	ICt_{50} (Human)	MCt_{50} (Human)
Sarin (GB)	100	75	3
Soman (GD)	70	Unknown	<1
Tabun (GA)	400	300	2–3
VX	50	35	0.04

LCt_{50}, concentration time function that kills 50% of exposed victims; ICt_{50}, concentration time function that incapacitates 50% of exposed victims; MCt_{50}, concentration time function that produces Miosis in 50% of exposed victims.
Adapted from Reference 10.

jects had no symptoms or laboratory findings indicating any exposure effects.

Even if skin decontamination has taken place, continued absorption from the inner layers of the skin can result in a delayed onset of symptoms. The onset of symptoms from dermal exposure to small amounts of nerve agent liquid has occurred as long as 18 hrs after exposure (8). The symptoms have usually been minor. As a general rule, the longer the time interval between the exposure and the onset of symptoms, the less severe the effects will be. In other words, the time interval between the exposure and the onset of symptoms is inversely proportional to the severity of the signs and symptoms. Large liquid exposures can result in onset of symptoms within 1–30 mins. Disabling signs and symptoms from a dermal exposure can occur abruptly with little, if any, warning. For example, respiratory distress can rapidly ensue, despite a lack of miosis, as is usually the first sign after nerve gas exposure.

The location of dermal exposure can also play an important role. In one study that used equipotent doses of VX applied to the skin in different areas of the body, maximal inhibition of blood cholinesterase activity occurred at 5 hrs when applied to the head and neck region, at 7 hrs when applied to the extremities, and at 10 hrs when applied to the torso.

Ambient temperature also affects absorption. Decreased absorption occurs at lower temperatures and increased absorption occurs at higher temperatures. In fact, decontamination procedures at typical room temperatures, after exposures at very low temperatures (e.g., 0–36°F), resulted in enhanced absorption (10).

Large liquid exposures can result in the onset of symptoms within 1–30 mins. Symptoms from a dermal exposure can occur abruptly, with little, if any, warning.

Ingestion. The ingestion of nerve agents is highly unlikely except for the ingestion of droplets from a line or point source spraying device. Like dermal exposures, ingestions of nerve agents can have a delayed but abrupt onset of signs and symptoms. One study used 54 subjects who drank water to which VX had been added (8). The amount of VX and types of water varied. At a VX dose of 400 μg per 70 kg dissolved in distilled water, red blood cell (RBC) cholinesterase activity decreased to 22% of normal. When VX was given in a saline or a dextrose solution, maximal effects on RBC cholinesterase activity were seen in 2–3 hrs. Eating before drinking VX-contaminated water increased absorption.

Toxicodynamics

Acetylcholinesterase is a member of a family of enzymes that hydrolyzes esters. An ester is an alcohol connected (covalently bonded) to an acid. Choline is an alcohol and acetic acid is an acid. Acetylcholinesterase hydrolyzes acetylcholine into its constituents, choline and acetic acid. At physiologic pH (i.e., at the normal blood pH of 7.4), acetic acid (CH_3COOH) is ionized and exists mainly as acetate (CH_3COO^-) and the hydrogen ion (H^+) in aqueous solution.

Acetylcholinesterase has a unique Enzyme Convention Number (EC 3.1.1.7). The Enzyme Convention System assigns a unique number to each enzyme and is conceptually similar to a Chemical Abstracts Service Number for nonenzymatic chemicals. The acetylcholinesterase enzyme found in the nervous system is only one type of cholinesterase. Cholinesterases are also found in other organ systems. For example, RBCs have cholinesterase activity that is very similar to that in the nervous system. The RBC cholinesterase Enzyme Convention number is also 3.1.1.7. The activity of RBC cholinesterase that is found in the plasma, also called true cholinesterase or cholinesterase, can be measured relatively easily (because it is a blood test measured in a heparinized green top tube), in contradistinction to measuring nervous system acetylcholinesterase activity that requires a nerve or brain biopsy. Therefore, by measuring RBC cholinesterase activity, one can infer the activity of acetylcholinesterase in the nervous system. RBC cholinesterase activity correlates better with nervous system cholinesterase activity than plasma cholinesterase (11–13). Plasma cholinesterase (EC 3.1.1.8) is also called pseudocholinesterase or butyrylcholinesterase. Symptoms do not always correlate exactly with RBC cholinesterase inhibition. Unless activity is reduced to 50%, or lower, even minor symptoms might not be present (11).

Organophosphates and carbamates are cholinesterase inhibitors. Cholinesterase inhibitors block the activity of the enzyme acetylcholinesterase, resulting in acetylcholine accumulation at all cholin-

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Table 5. Signs and symptoms of poisoning caused by cholinesterase inhibitors

Peripheral Nervous System		Central Nervous System
Muscarinic	Nicotinic	
Diarrhea	Mydriasis	Confusion
Urination	Tachycardia	Convulsions
Miosis	Weakness	Coma
Bradycardia, bronchorrhea, bronchospasm	Hypertension, hyperglycemia	
Emesis	Fasciculations	
Lacrimation		
Salivation, secretion, sweating		

Adapted from Reference 38.

Table 6. Cholinesterase "aging" half-times for nerve agents

Name	Synonym	"Aging" Half-Time
Sarin	GB	≈ 5 hrs
Soman	GD	≈ 2 mins
Tabun	GA	> 40 hrs
VX	None	> 40 hrs

Adapted from Reference 38.

ergic receptors. This causes continued receptor stimulation, thereby producing the cholinergic toxidrome (Table 5).

Acetylcholine binds at muscarinic receptors and nicotinic receptors. Muscarinic receptors are located in the central nervous system and in the peripheral nervous system (PNS) at neuroeffector junctions (the connection between a nerve cell and a muscle, a gland, etc.) of the parasympathetic portion of the autonomic nervous system. Nicotinic receptors are located in the central nervous system, in the PNS sympathetic and parasympathetic ganglia, and in the neuromuscular junction. Cholinesterase inhibitors act at all these sites; that is, they act in the central nervous system and PNS, at both muscarinic and nicotinic sites. Therefore, the signs and symptoms caused by cholinesterase inhibitor pesticide poisoning consist not only of the typically remembered PNS muscarinic signs and symptoms (SLUDGE: salivation, lacrimation, urination, defecation, gastroenteritis, and emesis) but also PNS nicotinic signs and symptoms (MTWHF: mydriasis, tachycardia, weakness, hypertension, and fasciculations) and central nervous system nicotinic and muscarinic signs and symptoms (Table 5). The preferred muscarinic mnemonic is DUMBELS because it contains the "killer bees", that is, those effects that can be fatal (bradycardia, bronchorrhea, and bronchospasm). The wide distribution of acetylcholinesterase, at both nicotinic and muscarinic receptors throughout the PNS and central nervous system, can result in seemingly contradictory signs and symptoms.

Clinically, nicotinic signs often predominate early in the course of cholinesterase inhibitor poisoning. However, concurrent nicotinic and muscarinic signs and symptoms are often present in both the PNS and central nervous system. Later in the course of cholinesterase inhibitor poisoning, muscarinic signs and symptoms predominate. Severely poisoned patients can suffer the nicotinic effect of depolarizing neuromuscular blockade (fasciculations followed by flaccid, or floppy, paralysis), muscarinic PNS effects such as bradycardia, and central nervous system effects such as coma. Acute respiratory insufficiency is the primary cause of death in acute poisonings.

Carbamates bind reversibly to acetylcholinesterase. Organophosphates will bind irreversibly to acetylcholinesterase, unless the patient receives the antidote 2-pralidoxime (2-PAM) before "aging" occurs. Aging is the average time required for irreversible binding to occur between organophosphates and acetylcholinesterase. Aging can occur within minutes for soman or can take up to days for some commercial organophosphate pesticides (Table 6) (13, 14). Aging is discussed further with regard to 2-PAM administration in the treatment section.

Signs and Symptoms

The accumulation of acetylcholine at the muscarinic and nicotinic receptor sites produces a predictable clinical syndrome, a cholinergic toxidrome. Initial symptoms can actually result from local effects and not from systemic toxicity. Because the dose that produces minimal effects is often only a little less than that capable of causing death, the presence or absence of various signs and symptoms can be misleading in regard to the correct diagnosis and prognosis.

Ocular System. Nerve agents may have variable effects on the eye, depending on the agent and route of exposure. Vapor exposure usually causes miosis, ocular pain, and dimmed or blurred vision. These are local effects and do not correlate with RBC cholinesterase activity, unless there has also been inhalational exposure (12). The duration of miosis is variable ranging from several days (to regain normal dilatory activity in indoor lighting) to as long as 9 wks to regain maximal dilation in total darkness (15, 16). Pain sometimes accompanies the miosis and is probably due to ciliary spasm. The discomfort can be characterized as a sharp or aching ocular pain and can be associated with a mild to severe headache (11). Sometimes the pain is accompanied by nausea and vomiting. Dermal or gastrointestinal absorption of nerve agents, particularly VX, can produce moderate signs and symptoms but not miosis (11, 17). Thus, the presence or absence of miosis does not provide good prognostic information.

Impaired visual acuity is a common effect from vapor exposure to nerve agents. Of the 15 physicians secondarily exposed to sarin vapors from the victims of the Tokyo subway incident, 73% complained of dimmed vision (15). The duration of effect, like that of miosis, can be variable, with normal vision returning in 48 hrs or taking as long as 35 days (16, 17). Tearing is not a reliable sign of early exposure to nerve agent vapor. Some eyes can have a bloodshot appearance caused by subconjunctival vascular dilation (2).

Respiratory System. Rhinorrhea is generally considered a local effect after a vapor exposure but can be a manifestation of systemic toxicity. The rhinorrhea is often copious, much worse than nasal secretions from a cold or hay fever, and the severity is dose dependent (10, 11).

Depending on the dose, respiratory symptoms range from local effects (e.g., increased secretions or bronchoconstriction) to systemic effects (e.g., ventilatory muscle paralysis with apnea). Large exposures to nerve agent vapors can result in severe bronchiolar smooth muscle constriction, wheezing, copious secretions (bronchorrhea), and ventilatory failure. Although the ventilatory failure is caused, in part, by flaccid paralysis of

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ventilatory muscles, there is also greatly diminished respiratory drive from the central nervous system (11).

Cardiovascular System. Excessive levels of acetylcholine can have a profound effect on cardiac activity. The expected effect on the heart would be increased vagal tone with bradycardia and atrioventricular heart blocks, even third-degree atrioventricular block. In fact, the heart rate can actually increase because of increased sympathetic tone from acetylcholine accumulating in sympathetic ganglia and at the adrenal medulla. Sidell and Groff (11) described heart rate effects in 199 patients with mild to moderate nerve agent exposures who were treated at the Edgewood Arsenal Toxic Exposure Aid Station.

Only 6.5% had heart rates <64 beats/min, while 35% had heart rates >90 beats/min. Ventricular arrhythmias are uncommon. Torsade de pointes was reported in a dog study that used sarin and in humans following organophosphate poisonings (18, 19).

Nervous System. Dermal exposures often produce local neuromuscular effects, including sweating and subjacent muscle fasciculations. Higher doses can cause muscle weakness, fatigue, and even flaccid paralysis (10). After a large exposure, generalized fasciculations are common and can continue for some time after other acute signs have decreased (10).

The cardinal central nervous system signs and symptoms after exposure to large amounts of nerve agents are seizures, coma, and apnea. Depending on the dose and route, these conditions can develop within 1–30 mins after an initially asymptomatic period. Seizures can develop suddenly, last briefly, and resolve spontaneously, or seizures can be prolonged, with status epilepticus. Children may be more prone to seizures than adults. Apnea can also be abrupt in onset and does not resolve without antidotal therapy.

Exposure to small amounts of nerve agents can produce several nonspecific central nervous system effects. Victims of low-dose nerve agent exposures have complained of forgetfulness, insomnia, irritability, depression, impaired judgment, bad dreams, and inability to concentrate (10). These symptoms can occur in the absence of physical signs. Survivors of large-dose exposures can also develop these symptoms. Recovery can take 4–6 wks (10).

Skin and Mucous Membranes. Dermal application of a liquid nerve agent can produce localized sweating and fasciculations of the underlying muscle. Generalized sweating is a common systemic effect following prolonged or extensive dermal exposure or after inhalation (10).

Gastrointestinal System. Excess acetylcholine increases gastrointestinal motility and secretions. Nausea and vomiting are common findings after inhalation and dermal exposures. Nausea and vomiting are among the first signs after dermal exposure, and somewhat paradoxically, diarrhea is an infrequent finding for all routes of exposure. Of the 111 patients who survived the Tokyo subway sarin attack and were categorized as moderately to severely poisoned, only six (5.4%) had diarrhea (20). In contrast, nausea occurred in 60.4% and vomiting in 36.9% (20).

Liver. Sympathetic stimulation results in adrenal medullary stimulation that raises the concentrations of circulating epinephrine and norepinephrine, which in turn causes hyperglycemia because of glycogenolysis and gluconeogenesis.

Genitourinary System.

After large dermal exposures and after the inhalation of significant amounts of vapors, micturition can occur. However, no cases were reported in either of the two sarin terrorist attacks in Japan or in the cases previously presented (11, 17, 20, 21).

Tables 7 and 8 summarize the clinical signs and symptoms associated with nerve agent exposures by the two primary routes of exposure, inhalation and dermal.

Treatment

Decontamination. There are few well-designed studies on the efficacy of various decontamination protocols in the medical literature. Although generalizations can be made, pragmatic decisions will need to be made. Severe weather conditions could override theoretical considerations because the risk of hypothermia might be greater than the worst possible effect of the chemical. Mass victim incidents will limit the amount of time and resources available to treat any one patient. In these situations, self- or buddy assistance will be necessary. The recommended duration of decontamination could be drastically lessened to provide rapid decontamination of multiple victims in the field. Because the delay to decontamination could be more critical than the length of decontamination, it is plausible that with large numbers of victims, a 1-min rinse after removal of contaminated garments might be acceptable decontamination for 15 people in 15 min, rather than a "thorough" decontamination of only one person for 15 min. These real-life field conditions are taxing and require the assistance of clinical toxicology experts. Most of the contamination from solids or liquids is removed by taking off all garments and by a brief decontamination. The exact benefits of longer decontamination are intuitive but have not been proven in the medical literature. The potential toxicity of the agent should also be considered, especially for chemicals that are absorbable through the skin such as the nerve agents. Ensure adequate decontamination to prevent secondary contamination of downstream healthcare workers who will come into contact with the nerve agent victim.

Decontamination of the respiratory system is accomplished by removing the patient from the source of the airborne exposure. The most important method of decontamination is adequate ventilation. Therefore, ensure adequate ventilation and oxygenation.

Skin decontamination is not necessary if the exposure has been to vapor only. However, clothing exposed to nerve agent vapor can carry minute amounts of the agent and can cause minor secondary contamination. The medical staff of St. Luke's Hospital in Tokyo were minimally affected by the condensed vapor on vic-

Table 7. Signs and symptoms after acute inhalation exposure to nerve agents

Low-dose with mild effects
Eyes and nose are most affected by exposure
Miosis with eye or head pain
Dim or blurred vision
Conjunctival injection
Rhinorrhea
Bronchoconstriction with tightness in chest
Mild bronchosecretions
Medium-dose with moderate effects
Shortness of breath (moderate to marked dyspnea)
Coughing
Wheezing
Nausea
Vomiting
Fasciculations
Generalized feelings of weakness
High-dose with severe effects
Loss of consciousness
Seizures
Apnea
Flaccid paralysis
Death usually occurs within minutes

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Table 8. Signs and symptoms after acute dermal exposure to nerve agents

Low-dose with mild effects
Localized sweating at the exposure site
Fine muscle fasciculations at the exposure site
Miosis is NOT an early sign after dermal liquid contact and may not be present at all
Medium-dose with moderate effects
Nausea
Vomiting
Severe headache
Generalized fasciculations
Feelings of weakness
BEWARE, NO RESPIRATORY SIGNS OR SYMPTOMS ARE PRESENT, YET
High-dose with severe effects
Sudden loss of consciousness
Seizures
Flaccid paralysis
Apnea
Death

Table 9. Protocol for extemporaneous preparation of atropine sulfate for injection

Reconstitute 30 g of atropine sulfate USP powder in 30 mL of normal saline (1 g/mL)
Draw up 1 mL into a syringe
Attach a Millex .22 micron filter to the syringe
Add 1 mL (1 g of atropine sulfate) to a 500 mL container of normal saline (2 mg/mL)
OR
Add 1 mL (1 g of atropine sulfate) to a 1-L container of normal saline (1 mg/mL)

USP, U.S. Pharmacopeia.

tims' clothing (17). Medical staff complained only of symptoms and manifested no verifiable signs or laboratory abnormalities such as cholinesterase inhibition (17). Once victims have been removed from the vapor source, their clothing should be removed and double bagged; this is generally sufficient decontamination for vapor exposures.

Because of the volatility of the G agents, it is unlikely that liquid skin exposures will result in a significant amount of nerve agent on the skin when the victim reaches medical attention (11). In other words, exposed patients pose a relatively low risk of secondary contamination to rescuers. However, liquid nerve agents should be removed from the skin immediately to alter the absorption for the exposed patient. Since the nerve agents are inactivated by alkaline solutions, a neutralizing agent such as 0.5% sodium hypochlorite solution (one part household bleach plus nine parts water) is currently recommended by the U.S. Army. However, most U.S. fire departments use detergent and water only. Continued contact with a nerve agent, from wet clothing or hair, requires that the clothing be removed and the hair washed as soon as possible. After contact with nerve agents, both the skin and the hair should be washed with dilute bleach solution. If an isolated area of the skin has been exposed and local symptoms are evident, a pad soaked in 0.5% hypochlorite should be applied to the area for approximately 20 mins and then the area should be washed with water.

Eye contact with liquid nerve agents should be decontaminated by irrigating with large quantities of water or sterile saline solution. Irrigation of the conjunctival sac should continue throughout patient contact and during prehospital transport, if possible. If continuous decontamination of the eyes is not possible, workers should decontaminate at the scene before ambulance transport, for at least 20 mins. Use of Morgan lenses with an ophthalmic local anesthetic, such as proparacaine, can make decontaminating the patient's eyes easier for the patient and the healthcare provider.

The assessment of a nerve agent victim should focus on the patient's clinical condition and the route of exposure. Vapor exposure usually causes immediate symptoms. Symptom onset can be significantly delayed after dermal exposure, so these patients should be observed for many hours. No minimum, safe duration of observations has yet been established because of lack of clinical experience and clinical studies.

Resuscitation must begin immediately following a significant inhalational exposure. Life-threatening symptoms can begin less than 5 mins after exposure and death can occur within 5 mins after the onset of seizures and respiratory arrest. Atropine and 2-PAM are essential antidotes for the resuscitation and treatment of victims of nerve agent poisoning.

Atropine. Atropine is a symptomatic antidote for the muscarinic signs and symptoms of nerve agent poisonings (22). Atropine is a competitive antagonist at muscarinic receptors only and thus blocks the effects of acetylcholine at muscarinic receptors in the PNS and central nervous system. Therefore, atropine is a parasympatholytic. Atropine works only at the muscarinic receptors and cannot counteract acetylcholine's effects at nicotinic receptors in the PNS or central nervous system. Therefore, atropine cannot counteract fasciculations, weakness, flaccid paralysis, or respiratory arrest caused by neuromuscular blockade at nicotinic receptors. Atropine does not regenerate the poisoned acetylcholinesterase (i.e., it does not reactivate the inactivated acetylcholinesterase), and thus it is not curative.

The total doses of atropine for nerve agent poisoning are often much smaller than those needed to treat organophosphate insecticide poisoning. Organophosphate insecticides are more slowly metabolized and more lipid soluble. Consequently, they are cleared much more slowly from the body; therefore, the cumulative dose of atropine can reach much higher totals.

Atropine should be reserved to treat moderate to severe symptoms of nerve agent poisoning. Mild exposures resulting only in miosis do not require atropine because atropine does not reverse miosis and it can cause other problems because of its anticholinergic effects. Miosis and ciliary spasm with severe eye pain can be treated with topical homatropine ophthalmic drops, if necessary. Rhinorrhea generally does not merit atropine administration unless it is severe and interferes with patient management. Atropine can counteract soman-induced hypothermia, which is considered a muscarinic-receptor-mediated event (23).

Patients with mild respiratory distress can be observed for 15–30 mins to see if these effects diminish after removal from the source of exposure. If respiratory symptoms do not improve, then atropine, 1–2 mg intravenously or intramuscularly, can be given. The intravenous route

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is preferred, if possible. The intramuscular route is reserved for the prehospital, multiple-casualty setting or when intravenous access cannot be obtained. Moderate airway discomfort from bronchospasm and increased secretions should be treated with atropine, 1–2 mg intravenously or intramuscularly, and repeated as needed every 5–10 mins until ventilation is easy. Dried secretions are not the end point of therapy in mild to moderate poisoning. In severe cases of nerve agent poisoning, atropine can be given as an initial dose up to 6 mg intravenously or intramuscularly and then 2 mg intravenously or intramuscularly, every 5–10 mins, until ventilation is easy and secretions have dried. Intravenous administration is preferable.

The indications to treat children with atropine are the same as those in adults. Children's dosing of atropine must be adjusted for weight and age. The U.S. Office of the Surgeon General recommends the following doses for children (3):

Infant (<2 yrs old): 0.5-mg maximum single dose, repeated as clinically indicated.

Child (2–10 yrs old): 1.0-mg maximum single dose, repeated as clinically indicated.

Adolescent: 2.0-mg maximum single dose, repeated as clinically indicated. A cumulative dose of approximately 10–20 mg of atropine in the first 2–3 hrs postexposure usually can adequately control the symptoms.

Atropine is available in a variety of different injectable dosage forms, including single and multiple-dose vials, prefilled syringes, and auto-injectors. The U.S. Armed Forces use AtroPen auto-injectors containing 2 mg of atropine. These atropine auto-injectors are packaged with another auto-injector containing 2-PAM in units called Mark I kits. These kits and the single auto-injectors are being made available, on a limited basis, to the civilian community as part of the Chemical Stockpile Emergency Preparedness Program. These Mark I kits are available to some of the federal domestic preparedness programs such as the Metropolitan Medical Response System.

It has been recommended that hospitals stock at least 150 mg of atropine (22). In the event that atropine doses are depleted, extemporaneous preparation of concentrated atropine sulfate should be compounded for administration (Table 9). If true cholinergic excess exists, the administration of atropine should produce no ill effects. However, excessive amounts of atropine, either from giving too much to a symptomatic patient or from giving atropine to an unexposed person, can produce anticholinergic effects such as dry mouth, blurred vision, dilated pupils, urinary retention, tachycardia, and inability to sweat. These side effects are generally considered minor although they can last for 24–48 hrs. Physostigmine should not be administered to counteract the adverse effects of atropine in a nerve gas exposure.

Significant caution should be exercised when hypoxia is present in cases of severe nerve agent poisoning. Intravenous administration of atropine to animals with hypoxia caused by severe respiratory complications of nerve agent poisoning has produced ventricular fibrillation (11). Therefore, hypoxia should be corrected first, if possible, before atropine administration. However, atropine should not be withheld from a victim of severe nerve poisoning because of a concern about precipitating a life-threatening arrhythmia, especially if the victim is an apparently healthy young person with an otherwise healthy heart.

Children appear to tolerate large doses of atropine better than some adults. Following the Gulf War, a retrospective national survey was conducted on atropine auto-injector poisonings in Israeli children (24). Several hundred children received accidental doses of atropine, often in the finger or palm. The doses were up to 17 times higher than the standard, age-appropriate doses. About 50% experienced some systemic effects, but only 8% suffered from severe atropinization (24). There were no seizures, hyperthermia, or deaths associated with this accidental atropine intoxication (22).

2-PAM. 2-PAM is an oxime, a chemical that reacts with the nerve agent-inhibited cholinesterase enzymes to remove the nerve agent from the enzyme, allowing the cholinesterases to reactivate and metabolize acetylcholine. The timing of 2-PAM administration is critical because the binding of the nerve agents to cholinesterase can become irreversible with time. This irreversible binding is called aging. Once aging has occurred, the cholinesterase enzyme will never be able to metabolize acetylcholine. Aging occurs at different rates for different nerve agents (Table 6) (11). For VX, the RBC cholinesterase enzyme deactivates at roughly 0.5–1.0% per hour for the first 48 hrs. It takes approximately 5 hrs for 50% of the sarin-cholinesterase enzyme complex to age. In contrast, the soman enzyme complex is completely, irreversibly aged within <10 mins with 50% of the enzyme aged after only 2 mins.

2-PAM is recommended for all cases of moderate to severe nerve agent poisoning. The optimal dosage is dependent on the nerve agent, time since exposure, and the cholinesterase activity of the victim. One human study assessed regeneration of cholinesterase activity when intravenous 2-PAM was given 1 hr after sarin exposure. A 2-PAM dosage of 10 mg/kg reactivated 28% of RBC cholinesterase activity. A 2-PAM dosage of 20 mg/kg reactivated 58% of RBC cholinesterase activity. If therapy was delayed for 3 hrs and the dose reduced to 5 mg/kg, only 10% was reactivated, but if the dose was increased to 10 mg/kg, the reactivation was >50% (11). After exposure to VX, 2-PAM given in doses of 2.5–25 mg/kg from 0.5 to 24 hrs reactivated >50% of the inhibited enzyme (11).

Normally, 2-PAM is given intravenously in 1- to 2-g loading doses after exposure (in 250 mL of normal saline or D_5W), over 5–10 mins, for a 70-kg person. The U.S. Armed Forces issue an auto-injector containing 600 mg of 2-PAM for intramuscular self-administration. A total of three auto-injector syringes are issued to each person. The recommended dose of 2-PAM for nerve agent exposure is variable, depending on the route of exposure and the severity of the poisoning. The current U.S. Surgeon General recommendation for 2-PAM is a maximum single dosage of 30 mg/kg or 2 g (2). Higher doses (e.g., 4 g) may be necessary in severe cases (25). Sidell (11) suggested that 2-PAM can be given up to a maximum cumulative dose of 2.5 g over 1–1.5 hrs with additional doses repeated one or two times every 60–90 mins. Data on administration of 2-PAM to children are limited. One suggested routine for pediatric victims is to begin with a dose of 15–20 mg/kg given by slow intravenous infusion (3). 2-PAM is rapidly excreted unchanged in the urine, with 80–90% of an intramuscular or intravenous dose excreted within 3 hrs.

A continuous intravenous infusion of 500 mg/hr (5–10 $mg \cdot kg^{-1} \cdot hr^{-1}$ in pediatric patients) has been used successfully for organophosphate insecticide poisoning and should be given after the loading

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dose for at least 24 hrs in patients exhibiting moderate to severe nerve agent intoxication (26–28). The maximum daily infusion dose is 12 g in adults. Criteria to terminate a continuous 2-PAM infusion include resolution of signs and symptoms of intoxication and stabilization of cholinesterase levels. Once these criteria are met, the 2-PAM continuous infusion can be terminated. However, immediately before its termination, the healthcare worker should obtain cholinesterase levels. If the patient's signs and symptoms of intoxication recur, the healthcare worker should rebolus with 2-PAM and restart the continuous intravenous infusion for 24 hrs. If the patient's signs and symptoms do not recur, the cholinesterase levels should be checked 6 hrs after termination of the continuous 2-PAM infusion. If the patient does not exhibit any recurrence of signs and symptoms by 6 hrs and the patient's RBC or plasma cholinesterase level is within 10% and 20% respectively, of the level obtained 6 hrs previously, then the therapeutic end point is reached and further 2-PAM is unnecessary. Cholinesterase levels display significant intra-individual variability, with RBC and plasma cholinesterase levels varying 10% and 20%, respectively, from one blood draw to the next in a given individual without any organophosphate toxicity.

In a case of true cholinergic crisis, no side effects are expected from 2-PAM administration. When 2-PAM is given to healthy adults without nerve agent toxicity, it can cause brief side effects such as dizziness and blurred vision. Hypertension is the side effect of greatest concern. Hypertension can occur with normal doses and recommended infusion rates. At doses of 45 mg/kg, systolic pressures can increase by >90 mm Hg and diastolic pressures can increase by 30 mm Hg. These elevations can persist for several hours (11). Increasing the infusion time to 30–40 mins can minimize this potential side effect. Phentolamine, 5 mg intravenously, has been used to reduce excessive elevation of blood pressure in adults.

Oximes other than 2-PAM have been used. Obidoxime chloride (Chemical Abstract Service no. 7683-36-5 or 114-90-9) is a quaternary oxime used primarily in Europe for organophosphate poisoning; it may be useful for sarin or tabun exposure (29). In addition to its primary antidotal property of reactivating cholinesterase, it also exhibits weak anticholinergic activity. Its half-life is about 2 hrs. The adult dose is 250 mg given by slow intravenous administration. This dose may be repeated up to two times at 2-hr intervals, for a maximum daily dose of 750 mg. A 5-day course can be considered for severe exposure. A continuous infusion of about 0.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ up to a maximum dose of 750 mg daily has also been used (30). Pediatric dosing is 4–8 mg/kg, not to exceed 250 mg per dose. Side effects include nausea, vomiting, diarrhea, paresthesia, elevation of hepatic transaminases, and tachycardia (at doses >5 mg/kg).

Other Therapeutic Modalities. Nebulized ipratropium bromide can be used as adjunctive therapy in treating nerve gas bronchospasm (31). Benzodiazepines are useful in controlling seizures: Diazepam (10 mg intravenous or orally in adults or 0.2 mg/kg in pediatric patients) should be given to individuals with severe exposure to prevent seizures. Hemodiafiltration (4-hr tenure) followed by hemoperfusion was used successfully in one patient exposed to sarin after the Tokyo subway attack who was resistant to pharmacologic therapy (32).

Pre-Exposure Prophylaxis. Pyridostigmine bromide was used by soldiers during Operation Desert Storm for pretreatment in anticipation of nerve agent exposure. It has been suggested that use of this drug, in combination with atropine and 2-PAM chloride, can increase survival following exposure to nerve agents over that provided by atropine and 2-PAM therapy alone (33, 34). The dosage regimen was 30 mg orally every 8 hrs, for up to 7 days. About half of the military personnel noted mild gastrointestinal symptoms (including increased flatus, abdominal cramps, and soft stools). Of the 41,650 soldiers (6.5% were women) taking pyridostigmine bromide, the drug was discontinued in 28 (0.07%) soldiers because of adverse effects (including exacerbation of asthma, hypertension, allergic reactions, and intolerable gastrointestinal complaints) (33).

Recently, a dermal topical protective agent containing a 50:50 mixture of perfluoroakylpolyether and polytetrafluoroethylene has been used by military personnel wearing mission-oriented protective posture gear when chemical warfare is deemed possible. Known as "Serpacwa" (skin exposure reduction paste against chemical warfare agents), it is manufactured for the U.S. Army by McKesson Bioservices and is applied to the skin until a barely visible white film layer is present. Before its application, a dry towel should be used to remove perspiration, insect repellents, camouflage paint, or dirt from skin. Animal studies have demonstrated decreased toxicity of sulfur mustard, VX, soman, T-2 mycotoxins, and CS (a lacrimator) (35, 36). Serpacwa's duration of action has not been evaluated for >6 hrs. Its major side effect is an occasional, mild flu-like syndrome. There is no systemic absorption through intact skin, but it has not been studied in pediatric patients. Standard decontamination techniques should still be followed after a nerve agent or other chemical agent exposure (36).

A focused, organized approach to the treatment of nerve agents is key to its successful management.

CONCLUSION

A focused, organized approach to the treatment of nerve agents is key to its successful management. Priority to decontamination (when appropriate), primary survey and resuscitation, and timely administration of atropine and 2-PAM are the main components to the poison treatment paradigm of these toxins. The local poison control center can serve as a valuable resource for recognition, protection, detection, triage, treatment, and antidote retrieval in the setting of mass nerve gas exposure (37).

Addendum

The preceding was adapted from the Advanced Hazmat Life Support manual (38). Advanced Hazmat Life Support (AHLS), a 2-day continuing education program, held its first course in October 1999 and has continued to grow into an international program. AHLS is based in the United States at the University of Arizona Emergency Medicine Research Center and is cosponsored by the American Academy of Clinical Toxicology. AHLS trains medical personnel including paramedics, physicians, nurses, pharmacists, and toxicologists in the medical

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management of people exposed to hazardous materials, including nuclear, biological, and chemical terrorism.

Courses are offered throughout the United States, Canada, and Australia. Check our Website for more information and a listing of all courses at www.ahls.org, or contact the International Headquarters at 520-626-2305, ahlsinfo@aemrc.arizona.edu, for more information.

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