Nerve Agents

The nerve agents are tabun (GA), sarin (GB), soman (GD), and VX. Nerve agents are the most toxic of all the weaponized military agents. These agents can cause sudden loss of consciousness, seizures, apnea, and death. Sarin (GB), one of the more commonly stockpiled nerve agents, may be inhaled as a vapor, or cause toxic effects by contact with the skin in the liquid form. VX is mainly a liquid skin hazard at normal ambient temperatures. These chemicals are easily absorbed through the skin, eyes, and lungs.

The diagnosis of a nerve agent poisoned casualty must be made clinically on the basis of the presenting signs and symptoms: **sudden loss of consciousness, seizures, apnea, and death**. There usually is not time for laboratory confirmation. Nerve agents inhibit cholinesterase, an enzyme present in tissues and blood. There is a laboratory blood test to determine cholinesterase activity.

Characteristics
The nerve agents belong to a class of chemicals called organophosphates and have a physiological effect similar to that of many insecticides commonly found in the community, such as malathion, diazinon, and chlorpyrifos. If organophosphate poisoning is not treated with appropriate antidote, the effect on cholinesterase is permanent.

Included among the nerve agents are chemicals called carbamates, which include some drugs (such as physostigmine and pyridostigmine) and some insecticides (Sevin7, Raid, etc.). These compounds cause the same clinical effects as the nerve agents developed for military use, but the latter are more than a hundred-fold more potent. Also, with carbamates, the effect on cholinesterase is only temporary.

Nerve agents are stored and transported in the liquid state. The G-agents such as sarin (GB), soman (GD), and tabun (GA) are volatile liquids at normal temperatures although, the most volatile, sarin, evaporates at about the same rate as water. In liquid form, the G-agents can be absorbed through the skin and eyes; vapor is absorbed by inhalation and through the eyes, but not through the skin unless the concentration of vapors is extremely high. The G-agent liquids are more effective in penetrating skin when the chemical is trapped between the skin and clothes. GB rapidly evaporates and is considered to be a “non-persistent agent,” meaning that it does not remain on terrain or equipment very long. VX is a persistent agent due to its low volatility. Though liquid at normal temperatures, VX has the consistency of motor oil, and seldom presents a vapor hazard, unless exploded or subjected to high temperature. VX is much more toxic (100 to 150 times) than sarin when on the skin because sarin evaporates from the skin surface while VX does not.

Mechanism of Action
Nerves communicate with muscles, glands, and other nerves by releasing chemicals (neurotransmitters) at their connection sites (synapses). One of the most common neurotransmitters is acetylcholine (ACh), which is released and collects at the receptor site stimulating the end organ to respond and produce a variety of effects: muscle contractions, gland secretions, and nerve□to□nerve conduction. These are known as cholinergic nerves and synapses.

When a nerve impulse reaches the synapse, ACh is released from the nerve ending and diffuses across the synaptic cleft to combine with receptor sites on the next nerve, muscle, or gland and stimulate a response.

To stop further stimulation of the nerve, muscle, or gland, ACh is rapidly broken down by the enzyme acetylcholinesterase (AChE) located in the postsynaptic receptor region, producing choline, acetic acid, and the regenerated enzyme. Thus, a check and balance system prevents

the accumulation of ACh and the resultant over-stimulation of nerves, muscles, and glands.

The term “nerve agent” refers to chemical that produces biological effects by inhibiting the enzyme AChE, thus allowing the neurotransmitter ACh to accumulate. As a result of inhibition of AChE, the neurotransmitter ACh accumulates and over-stimulates the receptors of the cholinergic nerves and causes hyperactivity of the cholinergic nerves, muscles, and glands.

Cholinergic synapses have two types of receptors: muscarinic receptors, nicotinic receptors, or a combination (central nervous system and cardiovascular system). Organs with muscarinic receptors include smooth muscles and exocrine glands; those with nicotinic sites are skeletal muscles and pre-ganglionic fibers.

Muscarinic receptors
Over-stimulation at muscarinic sites will increase glandular secretions. The victim may experience increased saliva, tearing, runny nose, thick secretions in the airways, and sweating; remembered by the acronym SLUDGE: salivation, lacrimation, urination, defecation and gastrointestinal emesis.

Smooth muscle over-stimulation
Over-stimulation of smooth muscles causes pinpoint pupils (miosis), bronchoconstriction of airways (shortness of breath), and hyperactivity of the gastrointestinal tract (nausea, vomiting, and diarrhea).

Nicotinic receptors
Over-stimulation of nicotinic receptors causes skeletal muscle fasciculations, twitching, cramping, weakness, and finally paralysis. There is also stimulation of the pre-ganglionic fibers, which may contribute to hypertension and tachycardia. **The combination of pinpoint pupils, muscle fasciculations and respiratory distress is reliable clinical evidence of organophosphate (nerve agent) poisoning.**

Cardiovascular
Cardiovascular effects that may occur are bradyarrhythmias and hypotension. Tachyarrhythmias (sinus tachycardia, ventricular tachycardia, and ventricular fibrillation), hypertension, and heart blocks may also occur. Most of these cardiovascular effects disappear once the antidote is given.

Central Nervous System
Acute severe effects include: loss of consciousness, seizures, and apnea. Effects from a mild exposure include: nervousness, fatigue, minor memory disturbances, irritability, and other minor psychological symptoms. The latter, whether caused by a severe or mild exposure, might linger for 4 to 6 weeks after exposure before resolving.

Cause of Death
The cause of death in nerve agent exposure is respiratory failure due to: bronchospasm and thick secretions in the airways; weakness of respiratory muscles to flaccid paralysis; and inhibition of the respiratory center in the CNS.

Clinical Effects

Vapor
After exposure to a small amount of vapor from a volatile nerve agent like GB, the most common effects are miosis - often with pain in the eye or head, complaints of dim or blurred vision or conjunctival injection, rhinorrhea, and some degree of bronchoconstriction and bronchosecretions with associated complaints of a tight chest and/ or shortness of breath.

After exposure to a moderate amount of vapor, besides the signs and symptoms noted above, the victim will show signs of multiple system involvement - especially increasing respiratory

distress and nausea, vomiting and diarrhea

After exposure to a large amount of vapor, the victim will almost immediately lose consciousness, and seizures will begin within 1 to 2 minutes. After several minutes of seizing, apnea and flaccid paralysis will occur.

Effects begin within a minute or so after vapor exposure and generally do not worsen significantly once the contamination is removed. Peak effects usually occur within the first 5 minutes following exposure.

If the exposure has been small and a victim is removed from the area of the exposure, shortness of breath may improve. In this situation, the removal of clothing is often adequate decontamination.

Liquid
Persistent agents like VX present more of a liquid contact hazard. The onset of effects following exposure can be delayed from 10 minutes to 18 hours after contact with the agent, depending on the dose. With military grade purity the LD 50 for VX is 10 mg, a droplet the size of the head of a pin. Fortunately, terrorists are unlikely to achieve such purity (the sarin at the Tokyo incident was a 20-40 % solution).

- small dose - A very fine droplet on the skin will cause fasciculations and diaphoresis under the droplet site. There will be no pinpoint pupils.
- moderate dose - With a larger droplet multiple system effects will occur including gastrointestinal (GI), nausea, vomiting, and diarrhea. Generally, there will be no pinpoint pupils.
- large dose - A droplet the size of the LD50 on the skin will cause sudden loss of consciousness, seizures, flaccid paralysis, and apnea within minutes.

Medical Management

Self-protection
The process of treating nerve agent casualties may be divided into several components. The first and most important concept is to protect oneself. Although liquid contaminated casualties are unlikely to present directly to the hospital ED prior to decontamination by emergency responders, medical personnel should always protect themselves by assuming the presence of liquid contamination, unless a clear vapor□only exposure history is obtained. Whenever possible, areas of liquid contamination should be decontaminated prior to patient handling to minimize spread of contamination and cross□contamination of other providers.

Decontamination
In the immediate aftermath of the sarin nerve agent attack in Tokyo, over 650 patients presented to St. Luke's Hospital within several hours after the release of sarin. With high numbers of vapor-exposed patients presenting to a medical facility under these conditions, minimum decontamination should include removal of patients' clothing and jewelry. This will hopefully prevent secondary chemical exposure of hospital personnel due to vapor off□gassing. If the patient has been exposed to liquid nerve agent (such as spraying or an explosion), survivors will require complete decontamination of skin and hair with water, soap and water, and water rinse at the scene prior to evacuation.

Patients arriving at the ED with an unclear exposure history who are symptomatic from nerve agent exposure should be fully decontaminated as above before entering treatment areas.

Airway and ventilation
Establishment of a patent airway is essential for the survival of the severely exposed patient.

Severely intoxicated patients will die if aggressive airway management is not quickly available. With large numbers of victims, rapid scene and resource assessment will influence triage decisions regarding interventional therapy. Because of the intense bronchoconstriction and secretions associated with nerve agent exposure, effective ventilation may not be initially possible due to high airway resistance (50 to 70 cm H2O). Adequate atropinization will reverse these muscarinic effects; therefore, atropine should be administered before any other measures are attempted. Endotracheal intubation, followed by positive pressure ventilation with a bag□valve mask, should be performed as quickly as possible. Periodic suctioning of secretions will help to improve ventilation and air exchange. Patients with seizures and respiratory failure can be saved with immediate and adequate intervention.

Antidote administration
Three medications are used to treat the signs and symptoms of nerve agent intoxication: atropine sulfate, pralidoxime chloride, and diazepam. The general indications for use of these antidotes will be presented first, followed by a discussion of their use in the treatment of mild, moderate, or severe nerve agent intoxication.

Atropine
Atropine works to block the effect of the accumulated neurotransmitter, ACh, at muscarinic sites. The more ACh at the sites, the more atropine is required to counteract its effects. Atropine can be administered intravenously (IV), intramuscularly (IM), or endotracheally (ET). Parenteral atropine will reverse muscarinic effects such as rhinorrhea, salivation, sweating, bronchoconstriction, bronchorrhea, nausea, vomiting, and diarrhea.

The IV route of atropine administration is preferred but can be also given intramuscularly (IM) or intrathecally but only until IV access is established.

> The initial parenteral dose of atropine is 2 to 6 mg in the adult, with subsequent doses titrated to the severity of the nerve agent signs and symptoms. Treatment for chemical nerve agent exposure might require up to 40 mg of atropine. Patients poisoned with insecticides may require these large doses; over 1,000 mg of atropine have been used. When atropine therapy exceeds the amount necessary to reverse the effect of the cholinergic hyperstimulation, it may cause toxicity manifested by dry mouth, flushing, and diminished sweating, but this would be extremely unlikely in a patient poisoned by an organophosphate (OP) compound. Side effects in unexposed people (not poisoned by OP compounds) include mydriasis, blurred vision, tachycardia, and diminished secretions. The latter (i.e., loss of sweating) may be of concern in a hot environment. Glycopyrrolate is a poor substitute and should not be used if atropine is readily available.
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> Atropine dosing is guided by the patient's clinical presentation and should be given until secretions are dry or drying and ventilation becomes less labored. When shortness of breath, increased airway resistance, and secretions have abated and the patient is breathing easier, he or she has received enough atropine. Heart rate and pupillary size, ordinarily accurate reflections of atropine dosing, are not useful for clinical monitoring after nerve agent exposure.
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> Atropine will not reverse nicotinic effects such as fasciculations, twitching, or muscle weakness. Nor are miosis or ciliary body spasm reversed by parenteral atropine; relief of intractable pain in or around the eye requires the installation of one percent homatropine topically.

Pralidoxime chloride (2-PAMCl)
This is an antidote that can specifically break the bond between the nerve agent and the enzyme AChE and thus remove the agent. This will free the enzyme, making it once again available to break down ACh. Clinically, this will decrease muscle twitching, improve muscle strength, and allow the patient to breathe easier; however, it has little effect on the muscarinic effects

described previously. The bond between the enzyme and the nerve agent can “age,” that is, the enzyme and agent become irreversibly bound. This means that if the antidote is not administered within 4 to 6 hours after sarin exposure (the aging time for the sarin□enzyme complex) or within 60 hours after VX exposure (the aging time for the VX-enzyme complex), the bond becomes permanent. Usually, there is plenty of time to treat patients with 2-PAMCl after exposure to nerve agents with the exception of GD. The soman□enzyme complex ages in about 2 minutes. Since pralidoxime takes time to take effect, atropine administration is the first priority.

MARK I kit
Includes atropine and pralidoxime chloride (2-PAMCl) and is used by the military in autoinjectors which together are called the MARK I kit. The atropine autoinjector contains 2 milligrams (mg) of atropine and is administered IM by pressing the end of the device onto the thigh. A spring pushes the needle into the muscle and causes the atropine to be injected. This device causes atropine to be absorbed more rapidly than when administered by a conventional needle and syringe. The other autoinjector contains 600 mg of 2-PAMCl. The Food and Drug Administration (FDA) has approved the autoinjectors for civilian use and Los Angeles County first responder EMS units have caches of these for field use. The Mark 1 is for healthy adult use only.

Diazepam
Seizures are treated with benzodiazepines such as diazepam. These medications can be used IV or via an autoinjector which contains 10 mg of diazepam. Some authorities recommend treating all severely exposed patients with diazepam whether they are convulsing or not. If three atropine MARK I kits are required initially, because of the victim’s clinical presentation, diazepam should be administered immediately thereafter. Diazepam should be given liberally and dosages may total 40 mg or more.

Treatment

Latent effects
Victims who present to the ED alleging exposure to nerve agents should be considered potentially exposed, triaged for anxiety and other injuries, and observed for up to 1 hour if a vapor exposure is alleged, or up to 18 hours if a liquid exposure is possible (or if the exposure history is uncertain).

Mild effects
If there are mild effects from liquid exposure (localized sweating and fasciculations at the site of liquid contact), give 600 mg 2□PAMCl IM (MARK I kit) or 1 gram (gm) 2-PAMCl IV slowly over 20 to 30 minutes. The presence of miosis and rhinorrhea requires observation only. If the victim is suffering from airway effects (shortness of breath, chest tightness, and profuse airway secretions) that are not improving, then treat with 2 mg of atropine IM or IV, or with the MARK I kit. Supplemental oxygenation will be needed only in those patients with pulmonary or cardiac disease. IM atropine dosing can be repeated at 5 to 10 minute intervals as needed.

> Note: Patients with pinpoint pupils may have severe light sensitivity and pain, but only require reassurance since these symptoms will resolve. At the hospital, these patients should be given a topical eye medication (homatropine) only for relief of severe pain in the eye(s) or head because the drug causes blurred vision. This may be done if miosis occurs as part of moderate or severe systemic effects as well.

Moderate vapor exposure

Be more aggressive with moderate vapor exposures.
Symptoms include those for mild exposures with more severe respiratory distress and may be accompanied by muscular weakness and possibly GI effects (vomiting and diarrhea). Initial dose for these patients is 1 or 2 MARK I kits containing a total of 2 mg atropine and 600 mg

2-PAMCl. Treatment may also be given IV, with 2 to 4 mg Atropine given IV push, and 1 gram of 2-PAMCl given by IV infusion slowly. This dosing can be followed by repeat doses of 2 mg of Atropine at 5 to 10 minute intervals as needed, and 600 mg of 2-PAMCl for a total of 1,800 mg 2□PAMCl with the MARK I kit IM (or 1 gm 2-PAMCl IV for a total of three doses at hourly intervals).

Antidotes can also be given IV, with Atropine given in 2 mg increments at 5 to 10 minute intervals, and 2-PAMCl given by infusion, 1 gm over 20 to 30 minutes, for a total of 3 doses at hourly intervals.

Moderate liquid exposure
Symptoms will include increasing respiratory distress and nausea, vomiting and diarrhea. For moderate toxicity several hours after liquid exposure, 2 mg of atropine and 600 mg 2-PAMCl should be given initially. Repeated doses of atropine and 2-PAMCl may be necessary. Oxygen may be needed in those with cardiac or pulmonary disease who have severe breathing difficulty.

Severe vapor or liquid exposure
Severe exposure symptoms will include all the above plus unconsciousness, seizures, apnea, or severe effects in two or more systems (excluding the eyes). Give 3 Mark 1s and diazepam and manage the airway. Repeat atropine at 5-10 minute intervals as necessary and 2-PAMCl in one hour.

Treatment for Nerve Agent Exposure

Exposure	Clinical	Treatment
Latent	None	None, observe for 1 hour with vapor and for 18 hours if liquid or unknown exposure
Mild	Miosis with dim and/or blurred vision, rhinorrhea, shortness of breath.	Miosis and rhinorrhea, observation only. Shortness of breath: one MARK 1 kit or Atropine 2 mg IM/IV and 2-PAMCl 600 mg IM or 1 gm IV.
Moderate	Above, but more severe; or vomiting and diarrhea	One MARK 1 Kit or Atropine 2mg IM/IV and 2-PAMCl 600 mg IM or 1 gm IV. Repeat 2 mg Atropine at 5-10 minute intervals until agent effects diminish.
Severe	Above plus unconsciousness, Flaccid paralysis, respiratory distress, cyanosis, seizures or severe effects in two or more organ systems	Oxygen, bag mask, intubate after three MARK 1 kits or Atropine 6 mg IM and 2-PAMCl 1800 mg IM or 1 gm 2-PAMCl IV repeated twice at hourly intervals. Repeat 2 mg Atropine at 3-5 minute intervals until atropinized. Diazepam for seizures

Age-Related Antidote Administration

Atropine
Certain members of the population may be more sensitive to Atropine. These include infants, young children, and the elderly. Pediatric experts have divided the age groups for IM administration of Atropine. These doses may be repeated as clinically indicated.

Category/Age Dose

- Infant - 0 to 2 years - 0.5 mg single dose
- Child - 2 to 10 years - 1.0 mg single dose
- Adolescent - young adult - 2.0 mg single dose
- Elderly - frail or medically compromised adult - 1 mg and repeat as necessary

If Atropine is to be given IV, then the dose for infants through young adults is 0.02 mg/kg.

If only standard MARK I kits are available, the use of a 2 mg Atropine autoinjector can be used, but infants and small children are at risk of being injured by the autoinjector needle. The most significant adverse effect of high dose Atropine in the younger patient is the inhibition of sweating.

Pralidoxime chloride
(no data available for 2-PAMCl use in children exposed to nerve agents)
Dose may be adjusted in the elderly; frail, hypertensive, or with renal disease, using one-half the usual adult dose of 2-PAMCl (7.5 mg/kg IV). If hypertension becomes significant during the administration of the 2-PAMCl, treat with IV phentolamine as follows: Adults - 5mg IV, Pediatrics - 1 mg IV

Category/Weight	IV dose	Weight	IM dose
Infant ≤ 70 kg	15 mg/kg repeated twice at hourly intervals	< 20	15 mg/kg
Above 70kg	1 gm repeated twice at hourly intervals PRN	> 20 kg	600 mg autoinjector

Diazepam

Recommended Pediatric Dose	
Infants > 30 days to ≤ 5	0.2 to 0.5 mg/kg IV slowly every 2 to 5 minutes to maximum dose of 5 mg
Children > 5 years	1 mg IV every 2 to 5 minutes to maximum dose of 10 mg