

## Chapter 4

# NERVE AGENTS

### Summary

*NATO Codes:* GA, GB, GD, GE, VX

***Signs and Symptoms:***

*Vapor, small dose:* miosis, rhinorrhea, mild difficulty breathing.

*Vapor, large dose:* sudden loss of consciousness, convulsions, apnea, flaccid paralysis, copious secretions, miosis.

*Liquid on skin, small to moderate dose:* localized sweating, nausea, vomiting, feeling of weakness.

*Liquid on skin, large dose:* sudden loss of consciousness, convulsions, apnea, flaccid paralysis, copious secretions.

***Field Detection:*** Joint Chemical Agent Detector (JCAD), M256A1 Chemical Agent Detector Kit, M18A2 Chemical Agent Detector Kit, M8 Chemical Agent Detector Paper, M9 Chemical Agent Detector Paper, Improved Chemical Agent Monitor (ICAM), M93 series Fox Reconnaissance System, M21 Remote Sensing Chemical Agent Alarm (RSCAAL), M90 Chemical Warfare Agent Detector, M22 Automatic Chemical Agent Detection Alarm (ACADA).

***Decontamination:*** Reactive Skin Decontamination Lotion, soap and water, 0.5% hypochlorate solution.

***Management:*** Administer three Antidote Treatment Nerve Agent Autoinjectors (ATNAAs) and one Convulsive Antidote, Nerve Agent (CANA) to severe casualties; support airway for respiratory distress.

## **Overview**

Nerve agents are the most toxic of the known chemical agents. They are hazards in both liquid and vapor states and can cause death within minutes after exposure. Nerve agents inhibit acetylcholinesterase in tissue, and their effects are caused by the resulting excess acetylcholine.

## **History and Military Relevance**

Nerve agents were developed in pre-World War II Germany. Germany had stockpiles of nerve agent munitions during World War II but did not use them for reasons that remain unclear. In the closing days of the war, the United States and its allies discovered these stockpiles, developed the agents, and manufactured nerve agent munitions. The US chemical agent stockpile, which is in the process of being destroyed, contains the nerve agents sarin (GB) and VX.

Nerve agents are considered major military threat agents. The only known battlefield use of nerve agents was in the Iraq-Iran conflict. Syria's chemical agent stockpile is a major concern. Intelligence analysts indicate that many countries have the technology to manufacture nerve agent munitions.

## **Physical Characteristics**

Nerve agents are liquids under temperate conditions. When dispersed, the more volatile nerve agents constitute both a vapor and a liquid hazard. Others are less volatile and represent primarily a liquid hazard. The G-agents (agents discovered by Germany) are more volatile than VX. GB is the most volatile, but it evaporates less readily than water. GF is the least volatile of the G-agents.

Nerve agents can be dispersed from many types of ground- and air-based munitions as both a vapor and liquid. These include but are not limited to mortars, missiles, rockets, grenades, landmines, and spray tanks.

## Detection and Protection

The immediately dangerous to life and health concentrations of nerve agents are 0.0001 mg/m<sup>3</sup> for tabun (GA), 0.0001 mg/m<sup>3</sup> for GB, 0.0003 mg/m<sup>3</sup> for soman (GD), 0.0001 mg/m<sup>3</sup> for GF, and 0.0001 mg/m<sup>3</sup> for VX. Liquid G-agents turn M8 paper a gold yellow, and VX turns M8 paper dark green or olive green. M9 paper will turn pink, red, reddish brown, or purple when exposed to liquid nerve agents or vesicants but does not specifically identify either the class of agent or the specific agent. See Table 4-1 for detection threshold limits by detector and agent.

Because the odor of nerve agents may be faint or lost after accommodation, olfactory detection of the odor of fruit or fish is not a reliable indicator of exposure. The activated charcoal in the canister of the chemical protective mask adsorbs nerve agents present as vapor or gas, as does the charcoal in the chemical protective overgarment. The butyl rubber in the chemical protective gloves and boots is impermeable to nerve agents. Proper wear of the protective mask and the chemical protective ensemble affords full protection against nerve agents.

**Table 4-1. Threshold Limits for Nerve Agent Detection**

Detector	GA (Tabun)	GB (Sarin)	GD (Soman)	GF	VX
JCAD	1.0 mg/ m <sup>3</sup>	1.0 mg/m <sup>3</sup>	1.0 mg/m <sup>3</sup>	0.1 mg/m <sup>3</sup>	0.041mg/m <sup>3</sup>
M256A series	Unknown	0.05 mg/ m <sup>3</sup>	Unknown	Unknown	0.02 mg/m <sup>3</sup>
M90	< 0.1 mg/ m <sup>3</sup>	< 0.1 mg/m <sup>3</sup>			
ICAM	0.03 mg/ m <sup>3</sup>	0.03 mg/ m <sup>3</sup>	0.03 mg/ m <sup>3</sup>	0.03 mg/ m <sup>3</sup>	0.01 mg/m <sup>3</sup>
M22	0.001 PPM	0.002 PPM	0.002 PPM	Unknown	0.0009 PPM

ICAM: Improved Chemical Agent Monitor; JCAD: Joint Chemical Agent Detector; PPM: parts per million

## **Mechanism of Toxicity**

Nerve agents are organophosphorus cholinesterase inhibitors. They inhibit the butyrylcholinesterase in plasma, acetylcholinesterase in red blood cells, and acetylcholinesterase at cholinergic receptor sites in tissue. The three enzymes are not the same; even the two acetylcholinesterases have slightly different properties, although both have a high affinity for acetylcholine. Measuring blood enzymes provides an estimate of the tissue enzyme activity. After acute exposure to a nerve agent, the erythrocyte enzyme activity most closely reflects the activity of the tissue enzyme, but during recovery the plasma enzyme activity more closely parallels tissue enzyme activity.

After a nerve agent inhibits the tissue enzyme, the enzyme cannot hydrolyze acetylcholine, the neurotransmitter, at cholinergic receptor sites. Acetylcholine accumulates and continues to stimulate the affected organ. Organs with cholinergic receptor sites include the smooth muscles, skeletal muscles, central nervous system (CNS), and most exocrine glands. In addition, cranial efferents and ganglionic afferents are cholinergic nerves. The clinical effects from nerve agent exposure are caused by excess acetylcholine.

Muscarine will stimulate some of the cholinergic sites, and these are known as muscarinic sites. Organs with these sites include the smooth muscles and glands. Nicotine will stimulate other cholinergic sites, known as nicotinic sites, which are those in skeletal muscle and ganglia. The CNS contains both types of receptors, but the pharmacology in the CNS is more complex and less well understood. Atropine and similar compounds block the effects of excess acetylcholine more effectively at muscarinic sites than at nicotinic sites.

Some commonly used organophosphate and carbamate pesticides and some common therapeutic drugs (the carbamates pyridostigmine and physostigmine) also inhibit acetylcholinesterase and can be considered nerve agents. However, while the organophosphate pesticides cause the same biological effects as traditional nerve agents discussed here, there are some important differences in the duration of biological activity and response to therapy.

The attachment of the agent to the enzyme is permanent (unless removed by therapy). Erythrocyte enzyme activity returns at the rate of erythrocyte turnover, about 1% per day. Tissue and plasma enzyme activities return with synthesis of new enzymes. The rate of return of the tissue and plasma enzymes is not the same, nor is the rate the same for all tissue enzymes. However, the agent can be removed from the enzyme and the enzyme “reactivated” by several types of compounds, the most useful of which are the oximes. If the agent-enzyme complex has not “aged” (a biochemical process by which the agent-enzyme complex becomes refractory to oxime reactivation of the enzyme), oximes are useful therapeutically. For most nerve agents, the aging time is longer than the time before acute casualties will be seen by a healthcare provider. However, the aging time of the GD-enzyme complex is about 2 minutes, and the usefulness of oximes in GD poisoning is greatly decreased after this period.

## Clinical Effects

The initial effects of exposure to a nerve agent depend on the dose and route of exposure. The initial effects from a sublethal amount of agent by vapor exposure are different from the initial effects from a similar amount of liquid agent on the skin. The estimated amounts to cause certain effects in humans are shown

**Table 4-2. Comparative Nerve Agent Vapor Toxicity\***

Agent	LCt <sub>50</sub>	ICt <sub>50</sub>	MCt <sub>50</sub>
GA	400	300	2–3
GB	100	75	3
GD	70	Unknown	< 1
GF	Unknown	Unknown	< 1
VX	50	35	0.04

\*For this table, one concentration of VX = 50, and one concentration of GB = 100, meaning it would take 2 times more GB to have the same median lethal dose as one concentration of VX.

LCt<sub>50</sub>: median lethal concentration/time

ICt<sub>50</sub>: median incapacitation concentration/time

MCt<sub>50</sub>: median first noticeable effect (of miosis) concentration/time

**Table 4-3. Comparative Median Lethal Dose Values on Skin\***

Agent	Amount
GA	100
GB	170
GD	5
GF	3
VX	1

\*Refer to FM 3-11.9, *Potential Military Chemical/Biological Agents and Compounds*, for specific LD<sub>50</sub> information. For this table, one dose of VX = 1, and 170 doses of GB = 170, meaning it would take 170 times more GB to have the same median lethal dose as one dose of VX.

in Tables 4-2 (vapor) and 4-3 (liquid on skin). The large amounts of GA and GB required to produce effects after skin application reflect the volatility of these agents; they evaporate rather than penetrate the skin. However, if these agents are occluded and prevented from evaporating, they penetrate the skin very well. GB, the agent studied most thoroughly in humans, causes miosis, rhinorrhea, and a feeling of tightness in the throat or chest at a concentration of 3 to 5 mg•min/m<sup>3</sup>.

Exposure to a small amount of nerve agent vapor causes effects in the eyes, nose, and airways. These effects are from local contact of the vapor with the organ and do not indicate systemic absorption of the agent. In this circumstance, the erythrocyte cholinesterase may be normal or depressed. A small amount of liquid agent on the skin causes systemic effects initially in the gastrointestinal (GI) tract. Lethal amounts of vapor or liquid cause a rapid cascade of events culminating within a minute or two with loss of consciousness and convulsive activity, followed by apnea and muscular flaccidity within several more minutes.

### *Eye*

Miosis is a characteristic sign of exposure to nerve agent vapor. It occurs as a result of direct contact of vapor with the eye. Liquid agent on the skin will not cause miosis if the amount of liquid is small. A moderate amount of liquid may or may not cause miosis. A lethal or near-lethal amount of agent usually causes miosis.

A droplet of liquid in or near the eye will also cause miosis. Miosis will begin within seconds or minutes after the onset of exposure to agent vapor, but it may not be complete for many minutes if the vapor concentration is low. Miosis is bilateral in an unprotected individual, but occasionally may be unilateral in a masked person with a leak in one eyepiece.

Miosis is often accompanied by complaints of pain, dim vision, blurred vision, nausea, occasional vomiting, and the presence of conjunctival injection. The pain may be sharp or dull, in or around the globe, but most often there is a dull ache in the frontal part of the head. Dim vision is due in part to the constricted pupil, and cholinergic mechanisms in the visual pathways also contribute. The complaint of blurred vision is less easily explained, because objective testing usually indicates an improvement in visual acuity because of the "pin-hole" effect caused by the miosis (the "pin-hole" effect results from blocking peripheral light waves, which are most distorted by refractive error, from entering the eye, reducing the blur by allowing only the most central light rays to reach the retina and providing clearer vision). Conjunctival injection may be mild or severe, and occasionally subconjunctival hemorrhage is present. Nausea (and sometimes vomiting) is part of a generalized complaint of not feeling well. Topical homatropine or atropine in the eye can relieve miosis, pain, dim vision, and nausea.

### *Nose*

Rhinorrhea may be the first indication of nerve agent vapor exposure. Its severity is dose dependent.

### *Airway*

Nerve agent vapor causes bronchoconstriction and increased secretions of the glands in the airways in a dose-related manner. The exposed person may feel a slight tightness in the chest after a small amount of agent and may be in severe distress after a large amount of agent. Cessation of respiration occurs within minutes after the onset of effects from exposure to a large amount of nerve agent. This apnea is probably mediated through the CNS, although peripheral factors

(skeletal muscle weakness, eg, in the intercostal muscles, and bronchoconstriction) may contribute.

### ***Gastrointestinal Tract***

After absorption, nerve agents cause an increase in the GI tract's motility and an increase in secretions by the glands in the GI tract's walls. Nausea and vomiting are early signs of liquid exposure on the skin. Diarrhea may occur with exposure to large amounts of agent.

### ***Glands***

Nerve agent vapor causes increases in secretions from the glands it contacts, such as the lacrimal, nasal, salivary, and bronchial glands. Localized sweating around the site of liquid agent on the skin is common, and generalized sweating after a large liquid or vapor exposure is common. Increased secretions of the glands of the GI tract occur after systemic absorption of the agent by either route.

### ***Skeletal Muscle***

The first effect of nerve agents on skeletal muscle is stimulation, producing muscular fasciculations and twitching. After a large amount of agent, muscle fatigue and weakness is rapidly followed by muscular flaccidity. Fasciculations are sometimes seen early at the site of a droplet of liquid agent on the skin, and generalized fasciculations are common after a large exposure. These may remain long after most of the other acute signs decrease.

### ***Central Nervous System***

The acute CNS signs of exposure to a large amount of nerve agent are loss of consciousness, seizure activity, and apnea. These begin within a minute after exposure to vapor and may be preceded by an asymptomatic period of 1 to 30 minutes after contact of liquid with the skin.

After exposure to smaller amounts of nerve agent, CNS effects vary and are nonspecific. They may include forgetfulness, an

inability to concentrate fully, insomnia, bad dreams, irritability, impaired judgment, and depression. These may occur in the absence of physical signs or other symptoms of exposure. After a severe exposure, these symptoms occur upon recovery from the acute severe effects. In either case, they may persist for as long as 4 to 6 weeks. CNS effects do not include frank confusion and misperceptions (ie, hallucinations).

### ***Cardiovascular***

The heart rate may be decreased because of stimulation by the vagus nerve, but it is often increased because of other factors such as fright, hypoxia, and the influence of adrenergic stimulation secondary to ganglionic stimulation. Thus, the heart rate may be high, low, or in the normal range. Bradyarrhythmias such as first-, second-, or third-degree heart block may occur. The blood pressure may be elevated from adrenergic factors, but it is generally normal until the terminal decline.

## **Physical Findings**

Physical findings depend on the amount and route of exposure. After exposure to small to moderate amounts of vapor, there are usually miosis and conjunctival injection, rhinorrhea, and pulmonary signs, although the latter may be absent even in the face of mild to moderate pulmonary complaints. In addition to these signs, an exposure to a high Ct (concentration-time product) may precipitate copious secretions from the nose and mouth, generalized muscular fasciculations, twitching or seizure activity, loss of consciousness, and apnea. Cyanosis, hypotension, and bradycardia may be present just before death.

Exposure to a small droplet of liquid on the skin may produce few physical findings. Sweating, blanching, and occasional fasciculations at the site may be present soon after exposure, but may no longer be present at the onset of GI effects. After a large exposure, the signs are the same as after vapor exposure. Miosis is a useful sign of exposure to vapor but does not occur after a liquid exposure unless the amount of exposure is large or the exposure is in or close to the eye.

## Time Course of Effects

Effects from nerve agent vapor (Table 4-4) begin within seconds to several minutes after exposure. Loss of consciousness and onset of seizure activity have occurred within a minute of exposure to a high Ct. After exposure to a very low Ct, miosis and other effects may not begin for several minutes, and miosis may not be complete for 15 to 30 minutes after removal from the vapor. There is no latent period or delay in onset from vapor exposure. Effects may continue to progress for a period of time, but maximal effects usually occur within minutes after exposure stops.

A large amount of liquid on the skin causes effects (Table 4-5) within minutes. Commonly there is an asymptomatic period of 1 to 30 minutes, and then the sudden onset of an overwhelming cascade of events, including loss of consciousness, seizure activity, apnea, and muscular flaccidity. After small amounts of liquid agent on the skin, the onset of effects has been delayed for as long as 18 hours after contact. These effects are initially

**Table 4-4. Nerve Agent Effects: Vapor Exposure**

<b>Mild</b> <ul style="list-style-type: none"><li>• Eyes: miosis, dim vision, headache</li><li>• Nose: rhinorrhea</li><li>• Mouth: salivation</li><li>• Lungs: dyspnea (tightness in the chest)</li><li>• Time of onset: seconds to minutes after exposure</li></ul>	<b>Immediate Treatment</b> <ul style="list-style-type: none"><li>• <i>Self-aid</i>: one ATNAA</li><li>• <i>Buddy-aid</i>: stand by</li></ul>
<b>Severe</b> <p>All of the above, plus</p> <ul style="list-style-type: none"><li>• Severe breathing difficulty or cessation of respiration</li><li>• Generalized muscular twitching, weakness, or paralysis</li><li>• Convulsions</li><li>• Loss of consciousness</li><li>• Loss of bladder and bowel control</li><li>• Time of onset: seconds to minutes after exposure</li></ul>	<b>Immediate Treatment</b> <ul style="list-style-type: none"><li>• <i>Self-aid</i>: none; soldier will be unable to help self</li><li>• <i>Buddy-aid</i>: three ATNAAs and diazepam immediately</li></ul>

ATNAA: antidote treatment nerve agent autoinjector

**Table 4-5. Nerve Agent Effects: Liquid on Skin****Mild to Moderate**

- Muscle twitching at site of exposure
- Sweating at site of exposure
- Nausea, vomiting
- Feeling of weakness
- Time of onset: 10 minutes to 18 hours after exposure

**Severe**

- All of the above, plus
- Severe breathing difficulty or cessation of breathing
  - Generalized muscular twitching, weakness, or paralysis
  - Convulsions
  - Loss of consciousness
  - Loss of bladder and bowel control
  - Time of onset: minutes to an hour after exposure

**Immediate Treatment**

- *Self-aid*: one to two ATNAAs, depending on severity of symptoms
- *Buddy-aid*: stand by

**Immediate Treatment**

- *Self-aid*: none; soldier will be unable to help self
- *Buddy-aid*: three ATNAAs and diazepam immediately

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ATNAA: antidote treatment nerve agent autoinjector

gastrointestinal and are usually not life-threatening. Generally, the longer the interval, the less severe the effects.

## Differential Diagnosis

The effects caused by a mild vapor exposure, namely, rhinorrhea and tightness in the chest, may easily be confused with an upper respiratory malady or allergy. Miosis, if present, will help to distinguish exposure from these diseases, but the eyes must be examined in very dim light to detect it. Similarly, GI symptoms from another illness may be confused with those from nerve agent effects, and in this instance there will be no useful physical signs. History of possible exposure will be helpful, and laboratory evidence (decreased red blood cell cholinesterase activity), if available, will be useful to make the distinction. Diagnosis is easier in the severely intoxicated patient. The combination of miosis, copious secretions, and generalized muscular fasciculations in a gasping, cyanotic, and convulsing patient is characteristic.

## **Laboratory Findings**

Nerve agents inhibit the cholinesterase activity of the blood components, and estimation of this activity is useful in detecting exposure. The erythrocyte enzyme activity is more sensitive to acute nerve agent exposure than is plasma enzyme activity. The amount of inhibition of enzyme activity does not correlate well with the severity of local effects from mild to moderate vapor exposure. The enzyme activity with localized exposure may be from 0% to 100% of the individual's normal activity, causing miosis, rhinorrhea, and/or airway symptoms. Normal or nearly normal erythrocyte acetylcholinesterase activity may be present, with moderate local effects in the exposed tissue. At the other extreme, the enzyme may be inhibited by 60% to 70% when miosis or rhinorrhea is the only sign of exposure. Severe systemic effects generally indicate inhibition of the erythrocyte acetylcholinesterase by 70% to 80% or greater. Other laboratory findings will relate to complications. For example, acidosis may occur after prolonged hypoxia.

## **Medical Management**

Managing a casualty with nerve agent intoxication consists of decontamination, ventilation, administration of antidotes, and supportive therapy. The condition of the patient dictates the need for each of these measures and the order in which they are done. Decontamination is described elsewhere in this manual. Skin decontamination is not necessary after exposure to vapor alone, but clothing should be removed because it may contain trapped vapor.

The need for ventilation will be obvious, and the means of ventilation will depend on available equipment. Bronchoconstriction and secretions increase airway resistance (to 50 to 70 cm of water), making initial ventilation difficult. The resistance decreases after atropine administration, after which ventilation is easier. However, the copious secretions may be thickened by atropine, impeding ventilatory efforts and requiring frequent suctioning. In reported cases of severe nerve agent exposure, ventilation has been required from 0.5 to 3 hours.

Three drugs (atropine, pralidoxime chloride, and diazepam) are used to treat nerve agent exposure, and another (pyridostigmine bromide) is used as pretreatment for potential nerve agent exposure. Atropine is a cholinergic-blocking or anticholinergic compound. It is extremely effective in blocking the effects of excess acetylcholine at peripheral muscarinic sites. When small amounts (2 mg) are given to healthy individuals without nerve agent intoxication, atropine causes mydriasis, a decrease in secretions (including a decrease in sweating), mild sedation, a decrease in GI motility, and tachycardia. In the military, atropine is packaged in autoinjectors, each containing 2 mg. The atropine dose in three ATNAAs may cause adverse effects on military performance in an unexposed person, and amounts of 10 mg or more may cause delirium. Potentially, the most hazardous effect of inadvertent use of atropine (2 mg, intramuscular) in a young person not exposed to a cholinesterase-inhibiting compound in a warm or hot atmosphere is inhibition of sweating, which may lead to heat injury.

Pralidoxime chloride (2-PAMCl) is an oxime. Oximes attach to the nerve agent inhibiting the cholinesterase and break the agent-enzyme bond to restore the normal activity of the enzyme. Clinically, this is noticeable in organs with nicotinic receptors. Abnormal activity in skeletal muscle decreases and normal strength returns. The effects of an oxime are not apparent in organs with muscarinic receptors; oximes do not cause a decrease in secretions, for example. They also are less useful after aging occurs, but with the exception of GD-intoxicated individuals, casualties would be treated before significant aging occurs. In addition to the atropine autoinjectors, the ATNAAs contain an autoinjector of pralidoxime chloride (600 mg). Each soldier is issued three ATNAAs (Figure 4-1).

Diazepam is an anticonvulsant drug used to decrease convulsive activity and reduce the brain damage caused by prolonged seizure activity. Without the use of pyridostigmine pretreatment, experimental animals died quickly after superlethal doses of nerve agents despite conventional therapy. With pyridostigmine pretreatment (followed by conventional therapy), animals survived superlethal doses of soman but had prolonged periods of seizure activity before recovery. They later

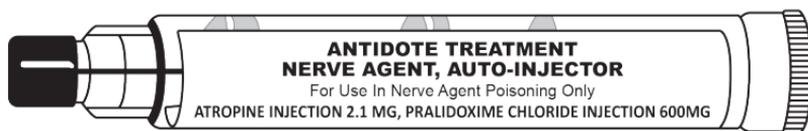


Figure 4-1. Antidote Treatment Nerve Agent Autoinjector (ATNAA).

had performance decrements and anatomic lesions in their brains. The administration of diazepam with other standard therapy to soman-exposed animals pretreated with pyridostigmine reduced the seizure activity and its sequelae. Current military doctrine is to administer diazepam with other therapy (three ATNAAs) at the onset of severe effects from a nerve agent, whether or not seizure activity is among those effects. In addition to the other autoinjectors, each soldier carries an autoinjector containing 10 mg of diazepam for administration by a buddy (soldiers who are able to self-administer would not need it). *Diazepam should be given if administration of three ATNAAs is required.* Medical personnel can administer more diazepam to a casualty if necessary. Medics may carry extra diazepam injectors (Figure 4-2) and are authorized to administer two additional injectors at 10-minute intervals to a convulsing casualty. (**NOTE:** Midazolam will replace diazepam in the CANA in the near future.)

The doctrine for *self-aid* for nerve agent intoxication states that if an individual has effects from the agent, one ATNAA should be self-administered. If there is no improvement in 10 minutes, a buddy should be sought to assist in the evaluation of the soldier's condition before further ATNAAs are given. If

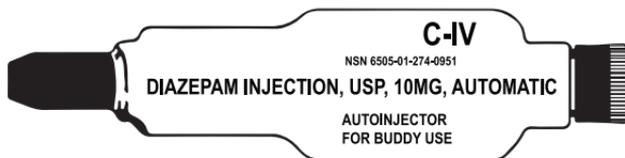
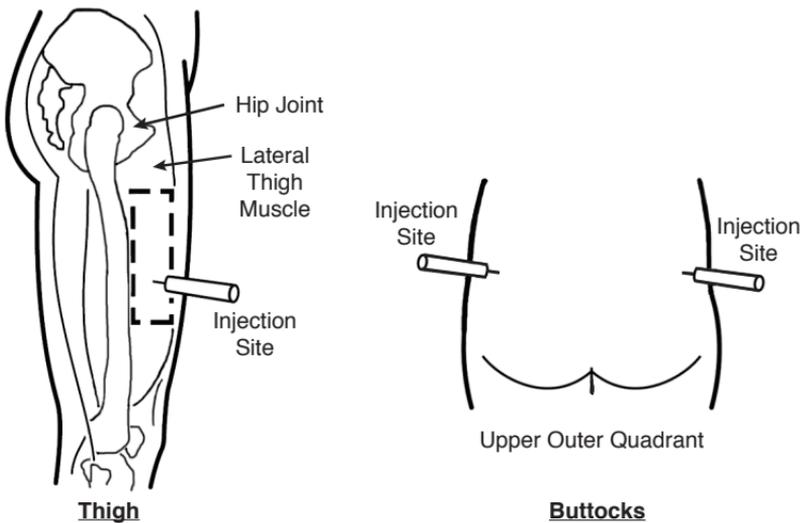


Figure 4-2. Convulsive Antidote, Nerve Agent (CANA) autoinjector.

a buddy finds an individual severely intoxicated (eg, gasping respiration, twitching) so he or she cannot self-administer an ATNAA, the buddy should administer three ATNAAs and diazepam immediately (Figures 4-3–4-6). The discussion below is advice for medical assistance.

The appropriate number of ATNAAs to administer initially to a nerve agent vapor casualty depends on the severity of effects. Systemic atropine will not reverse miosis (unless administered in very large amounts), and miosis alone is not an indication for an ATNAA. If the eye or head pain and nausea associated with miosis are severe, topical application of atropine (or homatropine) in the eye will bring relief. Topical atropine should not be used without good reason (severe pain), because it causes blurred vision for a day or longer. A casualty with miosis and rhinorrhea should be given one ATNAA only if the rhinorrhea is severe and troublesome (preventing the soldier from wearing a mask because of fluid). A casualty with mild to moderate dyspnea should be given one or two ATNAAs, depending on the severity of distress and the time between exposure and therapy. Respiratory distress



**Figure 4-3.** Primary (thigh) and secondary (buttocks) injection sites.



Figure 4-4. Self-aid injection.



Figure 4-5. Buddy-aid injection.

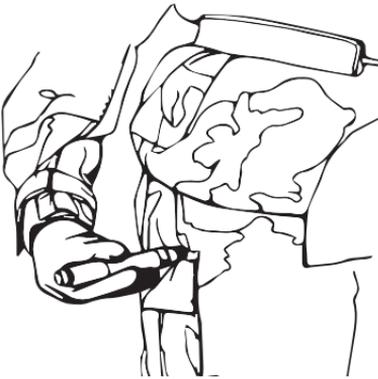


Figure 4-6. Hold the autoinjector like a pen.

from a mild exposure will spontaneously decrease within 15 to 30 minutes after termination of exposure, so if the casualty is not severely uncomfortable, only one ATNAA should be used initially. Atropine is quite effective, and care should be taken not to give too much to a casualty who does not need it.

A severe casualty of nerve agent vapor has miosis, copious secretions from the nose and mouth, severe difficulty breathing or apnea, possibly some degree of cyanosis, muscular fasciculations, and twitching or convulsive activity, and is unconscious. He or she should be given three ATNAAs and diazepam immediately. Ventilation will be needed and should be done via an endotracheal airway if possible. Suctioning of excessive airway secretions will be necessary to enhance air exchange and will make ventilatory efforts easier. Administration of atropine, in 2-mg doses, should be repeated at 3- to 5-minute intervals and should be titrated to a reduction of secretions and reduction of ventilatory resistance. When the IV preparation is available, the preferred route of atropine administration is via the IV route, but this route should be avoided until hypoxia is corrected, because intravenously administered atropine in hypoxic animals has produced ventricular fibrillation. In a hypotensive patient or a patient with tenuous venous access, atropine might be given intratracheally, either via the endotracheal tube or directly into the trachea, for more rapid absorption via the peribronchial vessels.

The medical care provider might overestimate the required atropine use in a mild to moderate casualty. More importantly, the care provider might underestimate atropine dosing by administering too little to a severe casualty. In a severe casualty, atropine should be pushed at frequent intervals until secretions are dry (or nearly dry) and until ventilation can be accomplished with ease. In reported cases this has required 10 to 20 mg of atropine within the first several hours. A conscious, less severely exposed casualty should receive atropine until breathing comfortably, and able to communicate this. Dry secretions need not be an endpoint in mild to moderate casualties.

The casualty with skin exposure to liquid is more difficult to evaluate and manage than is a vapor exposure casualty. Agent on the surface of the skin can be decontaminated, but agent

absorbed into the skin cannot be removed. The initial effects from absorbed liquid agent can start 2 to 3 hours after thorough decontamination of agent droplets on the skin. A casualty from liquid exposure on the skin may continue to worsen because of continued absorption of the agent from the skin depot.

The first effects of a liquid droplet on the skin are sweating with or without blanching, and occasionally muscular fasciculations at the site. GI effects (nausea, vomiting, and sometimes diarrhea) are the first systemic effects, and these may start from 0.5 to 18 hours after contact with the agent. If these effects occur within the first several hours after exposure, they may portend more severe effects, and initial therapy should be two ATNAAs. If effects begin later, initial therapy should be one ATNAA.

A large amount of liquid agent on the skin will cause effects 1 to 30 minutes after contact, whether or not decontamination was done. Nevertheless, early decontamination may lessen the magnitude of the effects. After the latent or asymptomatic period, the casualty will suddenly lose consciousness and begin seizure activity. The condition of the casualty and management are the same as described for a severe casualty of vapor exposure.

Further care of the severe casualty consists of atropine administration to minimize secretions and ventilation until spontaneous respiration resumes. Oxime administration should be repeated at hourly intervals for two or three additional doses. The preferred method of administration of the oxime is by IV drip of 1 g over 20 to 30 minutes (more rapid administration will cause hypertension), but three additional oxime autoinjectors (a total dose of 1.8 grams) may be given if the IV route cannot be used. The need for ventilation may continue for 0.5 to 3 hours. Unless prolonged hypoxia or other complications have occurred, the casualty will eventually begin having spontaneous muscular activity and make sporadic attempts to breathe. Muscles will become stronger and breathing more regular, and the casualty will have intermittent episodes of conscious behavior. Within an hour or two, these casualties will be breathing, moving, and conscious, although they will be weak and intermittently obtunded.

## Pretreatment

In late 1990s, the US military fielded pyridostigmine bromide as a pretreatment for nerve agent exposure. Each service member received a blister pack containing 21 30-mg tablets. The dose regimen is one 30-mg tablet every 8 hours. When to start and stop dosing is a division or corps' command decision, made with the advice of the intelligence, chemical, and medical staffs, and not a local decision or individual decision. Thus, pyridostigmine is, in a sense, not a medical treatment but a defensive weapons system.

Pyridostigmine bromide is the drug of choice for myasthenia gravis and has been approved for the treatment of this disease since 1951. In 2003 the US Food and Drug Administration approved additional on-label use of pyridostigmine bromide for pretreatment against soman. Consequently, commanders have the authority to order its use without service members' consent, exactly as they may order an approved vaccine.

Pyridostigmine is pretreatment, *not* an antidote. It should be taken before soman exposure. It is ineffective unless standard ATNAA therapy is also used in the appropriate manner. When given before soman exposure and when that exposure is followed by the standard ATNAA therapy, pretreatment increases the  $LD_{50}$  several fold over the  $LD_{50}$  that occurs without the use of the pretreatment. Functionally, this means that a soldier can survive what would otherwise have been a lethal dose; instead of dying, the casualty is a very sick patient who can be saved when antidotes are properly and promptly administered. When soman is the nerve agent, the use of pyridostigmine increases survival. When the agent is GB or VX, survival after standard ATNAA therapy is essentially the same whether or not pyridostigmine pretreatment is used; that is, pyridostigmine use provides no benefit in GB or VX poisoning. Current data are not adequate to evaluate the effectiveness of pyridostigmine pretreatment for GA or GF exposure. One consequence of the greater survival from the use of pyridostigmine is prolonged seizure activity and subsequent possible brain damage in the survivors. The early administration of diazepam will decrease these effects.

In the 1960s, it was noted that carbamates bind to the active site of cholinesterase in a similar manner as the binding of

organophosphonate cholinesterase inhibitors to cholinesterase. Additionally, while the carbamate is attached to the active site, an organophosphorus compound can not attach to the enzyme. The carbamate-enzyme binding, or carbamoylation, lasts only for hours, rather than for the lifetime of the enzyme as does the organophosphorus compound attachment, and is therefore spontaneously reversible. While the enzyme is carbamoylated, the active site is protected from attack by other compounds such as organophosphorus cholinesterase inhibitors, including nerve agents. After several hours, the carbamate leaves the enzyme (ie, decarbamoylation occurs), and the enzyme becomes completely functional again. Thus, the carbamate provides temporary protection for the enzyme against nerve agent attack. People have far more acetylcholinesterase than they need, so the use of pyridostigmine to carbamoylate a small proportion of acetylcholinesterase converts that proportion into a reserve that will be available to save the patient if soman attack inactivates the rest.

Many carbamates have been investigated for their effectiveness and their safety. Pyridostigmine was found effective and underwent extensive testing in humans. It has a 45-year safety record and is used by over 16,000 myasthenic patients in the United States on a daily basis. Investigations indicated that it did not interfere with the performance of military tasks and caused no adverse physiological disturbances.

Tens of thousands of US troops took pyridostigmine during the Persian Gulf War. The incidence of side effects (primarily GI and urinary) was over 50%, but only a few percent of the troops sought medical care for severity of these effects. Medical officers discontinued the drug in less than 1% of cases.

## Triage

A severe nerve agent casualty who is unconscious, convulsing or postictal, breathing with difficulty or apneic, and possibly flaccid will survive with appropriate, immediate therapy, including ventilation, if circulation is intact. This casualty should be triaged as *immediate* if therapy can be provided. If a blood pressure cannot be obtained, the casualty may be considered *expectant*.

Casualties with severe symptoms who are spontaneously breathing, have not lost consciousness, and have not seized have an excellent chance of survival with a minimal amount of therapeutic effort. They should be categorized as *immediate* and given three ATNAAs and diazepam. The casualty may worsen if exposure was to liquid, and atropine administration should be repeated. If the casualty loses consciousness, seizes, and becomes apneic, triage and administer further care based on available resources.

Casualties who are walking and talking and are no longer being exposed to agent will usually be triaged as *minimal*. If a casualty can walk and talk, then breathing and circulation are intact. There is no indication for immediate life-saving care. This does not preclude self-administration or medic administration of additional antidote for symptoms.

A casualty recovering from a severe exposure who has received large doses of antidotes and has been ventilated will be triaged as *delayed* for further medical observation or care. A casualty who suffered liquid exposure and has been both treated and decontaminated may also be triaged as delayed.

## Return to Duty

Return to duty depends on the status of the casualty, his or her assignment, and the tactical situation. Studies indicate that animals with decreased erythrocyte acetylcholinesterase activity from a nerve agent exposure have a decreased LD<sub>50</sub> for another nerve agent exposure (they are more susceptible to the agent) until that cholinesterase activity returns to at least 75% of its baseline, or to preexposure activity. Nerve agent-exposed workers in a depot or research facility are prevented from returning to work with agents until this recovery occurs. In a battlefield situation, conservative management should be balanced against the mission and the risk of repeated exposure to a large amount of agent.

In a military field situation, the capability to analyze blood for erythrocyte cholinesterase activity is usually not available, and the baseline activity of each individual is not known. The erythrocyte cholinesterase activity in a casualty with severe

systemic effects will be inhibited by 70% or greater (30% or less of preexposure activity), and 45 days or longer will be required for cholinesterase activity to return to 75% of preexposure activity. The enzyme activity of a casualty with mild or moderate effects from agent vapor may be nearly normal or may be markedly inhibited. Predictions of erythrocyte cholinesterase recovery time are unreliable.

Most individuals triaged as minimal may return to duty within hours if the mission requires these personnel, although lingering ocular and CNS effects may be limiting factors in these cases. These individuals may be able to fire a rifle, but their performance might be decremented because of both visual problems and difficulty in concentrating. These prolonged effects must be evaluated before the casualties return to duty.

Casualties who had severe effects might be walking and talking after 6 to 24 hours but may be unfit for most duties. Ideally, they should be kept under medical observation for a week or longer and not returned to duty until recovery of cholinesterase activity. However, the mission may lead to modification of these guidelines.

## **Long-Term Effects**

Minor electroencephalographic (EEG) changes were noted more than a year after nerve agent exposure when averaged EEGs in a group of individuals exposed to a nerve agent were compared to a control group. EEG changes could not be identified in individuals. Neuropsychiatric pathologies have been noted in individuals for weeks to months after exposure to insecticides. Both in the Tokyo subway attack and in the Iran-Iraq War, reports of long-term neuropsychiatric changes after exposure to nerve agent have surfaced. Little is known about the pathophysiology of these syndromes. They are not dose-related and do overlap with posttraumatic stress disorder.

Polyneuropathy, reported after organophosphate insecticide poisoning, has not been reported in humans exposed to nerve agents and has been produced in animals only at unsurvivable doses. The intermediate syndrome has not been reported in humans after nerve agent exposure, nor has it been produced in

animals. Muscular necrosis has occurred in animals after high-dose nerve agent exposure but reversed within weeks; it has not been reported in humans.

