Chemical Nerve Agents: The Most Sinister of Terrorist Weapons

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Background

Terrorism is a reality of life in the United States and abroad today. News reports frequently remind us of those groups and individuals who are intent on injuring and killing victims in the name of a cause, for personal satisfaction or power. The March 1995 Sarin nerve agent attack on the Tokyo subway system resulted in a heightened level of concern in the US for such an attack on domestic soil.

While there are a variety of options for terrorism in existence today, there are only a few that are likely for use in a non-military setting. Dr. Alexei Yablokov, an expert on nuclear security and former science advisor to President Boris Yeltsin testified before the National Security House Subcommittee in 1997 about the existence of "nuclear suitcase bombs" in the former Soviet Union, and the lack of knowledge of their current location (PBS, 1999). Each suitcase is attributed a one-kiloton nuclear weapon. It is assumed that nuclear weapons might be very difficult for a terrorist group to bring into the US and detonate. Radioactive materials could, however, be incorporated into an explosive device and thus constitute a greater threat, but this is also considered unlikely. Chemical and biological agents are much more likely to be used and thus are considered to be highly significant threats by the FBI. Of these, only chemical agents have been used in a non-military setting with significant consequences. It is now considered a question of "when," not "if" a terrorist using chemical weapons will strike in the US.

Nonconventional weapons have been used throughout history, albeit with less sophistication than today. The Greeks used a form of biological warfare in the fourth century BCE when they used animal corpses to pollute the wells used by the enemy. In the middle ages invading armies catapaulted bodies laden with plague and other diseases against besieged populations (Newark 1988). The United States joined Britain and France in using blankets laden with smallpox to infect the Native Americans prior to the American revolution. In World War I the use of biological and chemical weapons became important tools in the arsenal of continental armies. At Ypres, Belgium, the Germans instituted the first use of chemical agents in warfare. On April 22,1915 they released 168 tons of chlorine gas along enemy lines. Five miles of allied lines were opened, but the Germans did not expect such a result, and they did not take advantage of the success. They later implemented mustard gas also. There were approximately one million chemical casualties in WW I, with about 5% of those being fatalities.

Since the early 1970's there has been an increase in the number of terrorist threats in the United States and elsewhere. Many of these have involved the use of explosive devices, however the use of chemical or biological materials is increasing (figure 1). In 1972 a group called the Order of the Rising Sun were found to have 30-40 kilograms of typhoid bacteria cultures with which they intended to launch a terrorist attack on the water supplies of Chicago, St. Louis and other cities in the Midwest.

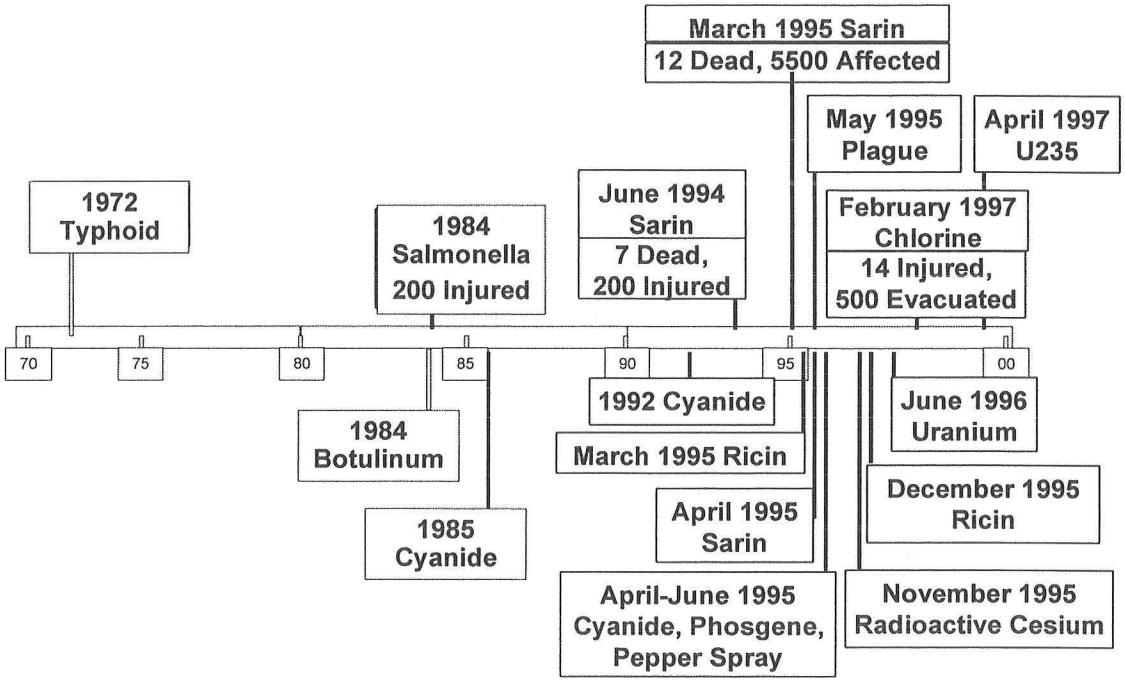


Figure 1 Chemical, biological and nuclear terrorist incidents in the United States and abroad. Soldier Biological and Chemical Command (SBCCOM), 1999 Domestic Preparedness Training program materials.

The 1984 attack by the Bhagwan cult was an attempt to influence local elections by spraying salmonella onto salad bars at community restaurants in Oregon. In that event 45 victims were admitted to area hospitals and 751 people became ill. No fatalities were reported.

These two events were more isolated in nature. In the 1990's the frequency of such terrorist acts has increased. Many of these incidents involved the use of powerful explosive devices, as noted in Table 1. Of particular note, however was the increase in the use of nuclear, biological and chemical (NBC) agents during this decade.

Table 1: Terrorist use of explosive devices in the United States, 1993-1997	
1993	World Trade Center bombing kills 6, injures 1,000
1995	Oklahoma City Bombing kills 168, injures 759
1996	Khobar Towers bomb kills 19
1996	Centennial Park bomb
1997	Clinic, night club – first use of secondary devices to injure responders

Aum Shinrikyo and the Japan sarin nerve agent attacks

In the early 1980's, a man named Chizuo Matsumoto changed his name to Asahara and established a small organization called the Aum Association of Mountain Wizards. After a trip to the Himalayas, in which he met the Dalai Lama, he felt that he was to establish a world religion and changed the name of his organization to Aum Supreme Truth or Aum Shinrikyo. This organization grew to tremendous proportions, achieving a membership of approximately 20,000 members. Estimates of the wealth of this organization approach $1 Billion. The group became entrenched in a siege mentality and required absolute submission to its leader, Asahara. The group carried out assassinations of opponents and developed facilities to manufacture deadly nerve agents and biological terrorist weapons. In June 1994 the group attempted to assassinate three judges in Matsumoto, Japan. These judges were considering the verdict in a lawsuit against the Aum cult. Arriving too late at the courthouse, the assassination team decided instead to release sarin nerve agent in the residential community where the judges lived. The attack involved a truck with a device to release sarin. Although the judges were not killed, 7 people died and 280 were injured. Initially, a resident in the neighborhood was blamed for the incident on the assumption that he had been mixing organophosphate insecticides in his garage. It took almost a year for this individual to clear himself of the incident. On March 20, 1995, after becoming alerted that the police were planning a raid on the organization, Aum Shinrikyo launched a pre-emptive attack on the Tokyo subway (Kaplan et al, 1996). They put low potency (dilute) sarin nerve agent into lunch boxes and other containers disguised as lunch bags. The terrorists used umbrellas with sharpened points to puncture the containers during the Monday morning rush-hour on 3 subway lines that were converging on downtown Tokyo. This tragic event caused 11 deaths and approximately 5,500 injuries among the commuters and emergency responders (Sadayoshi O et al, 1997). The nearest hospital, St. Luke's International Hospital saw 641 of the victims. Approximately 85% of the victims bypassed the emergency medical system (EMS) and presented directly to hospitals with no decontamination. Fortunately, the weekly grand rounds were taking place at St. Luke's hospital and the majority of the medical staff was present at the time patients began arriving (Okumura T et al, 1998). There were important delays in determining the identity of the poison involved and in reporting this information to the hospitals. Medical personnel began telephoning the poison center, but this agency had not been informed of the nature of the toxin. Initially it was assumed that the victims had been exposed to carbon monoxide or possibly cyanide vapor.

The incident was being watched on television by a physician in Matsumoto and he correctly noted that this was the same toxin that had been used in his city several months previously. He telephoned and faxed colleagues in Tokyo with his knowledge of the identity of the agent within 2 hours of the subway attack (Okumura et al, 1998).

The Tokyo sarin attack caused US officials to seriously question American preparedness for such an attack. Initially, comparisons were made between the nerve agents and the organophosphate insecticides. The concept was that a nerve agent attack in the US would be a lot like someone dumping a large amount of insecticide on an intersection in Dallas. This type of simplification is

misleading, however, because of the significant differences between the insecticides and the nerve agents. Indeed, there are important distinctions between the nerve agents themselves, as we will see below.

The sarin incident in Tokyo demonstrated a concept commonly discussed by disaster response planners that approximately 4/5 of victims will present directly to hospitals without the intervention of HAZMAT or other prehospital personnel. In the event of a toxic exposure, this is readily seen by a mental experiment in which the reader envisions him or her self at the scene of a deadly nerve agent release. People are running from the scene, and there are several people who are comatose or seizing. A typical time for response and set-up for a hazmat incident is approximately one hour. This time is a minimum realistic time because of the sequence of activities which must occur: notification, response, hot-zone and perimeter setup and initiation of victim triage. In most cases the person will not wait for emergency personnel to arrive on scene. Often the most realistic option would be to obtain private transportation.

As a result of the public self-referral to area hospitals, health facilities will require decontamination facilities, personal protective equipment (PPE), antidotes and disaster plans to respond to such an incident, and must not rely on EMS for these actions.

History of the nerve agents

The modern use of nerve agents began in World War II when the chemist Gerhard Schrader was working on the development of organophosphate insecticides (Sidell FR 1997). He was working for the German manufacturer I. G. Farbenindustrie in 1936 when he developed the first of these agents, Tabun (GA). This was followed by sarin, named for the initials of the scientists participating in its creation (GB) (Paxman HR 1982). The German Ministry of Defense required that substances with potential for military use be reported to the government, and Shrader complied with this regulation. Shortly thereafter a large production facility was built at Dyhernfurth. This facility produced tabun and sarin beginning in 1942 (Paxman Hr 1982, Robinson JP 1971). Towards the end of the war the Soviets captures the Dyhernfurth facility, dismantled it and moved it to the former Soviet Union where production continued (Robinson JP 1971).

Nerve agents: basic characteristics

First we will briefly review the mechanism of organophospate toxicity, in order to understand the biological effects of the nerve agents (figure 2). This general model for cholinesterase function diagrams the mechanism of acetylcholine metabolism. Acetylcholine, one of the most important neurotransmitters in the body gets attached to acetylcholinesterase by weak ionic bonds. At the esteratic site, acetylcholine is cleaved into two simple molecules: acetate and choline. This enzyme has one of the highest turnover numbers (number of substrate molecules that it catalyzes per unit time). Acetate goes into intermediate metabolism, and choline is taken up presynaptically and recycled by combination

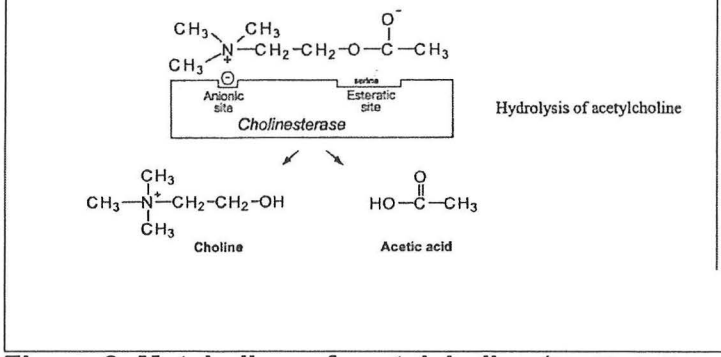
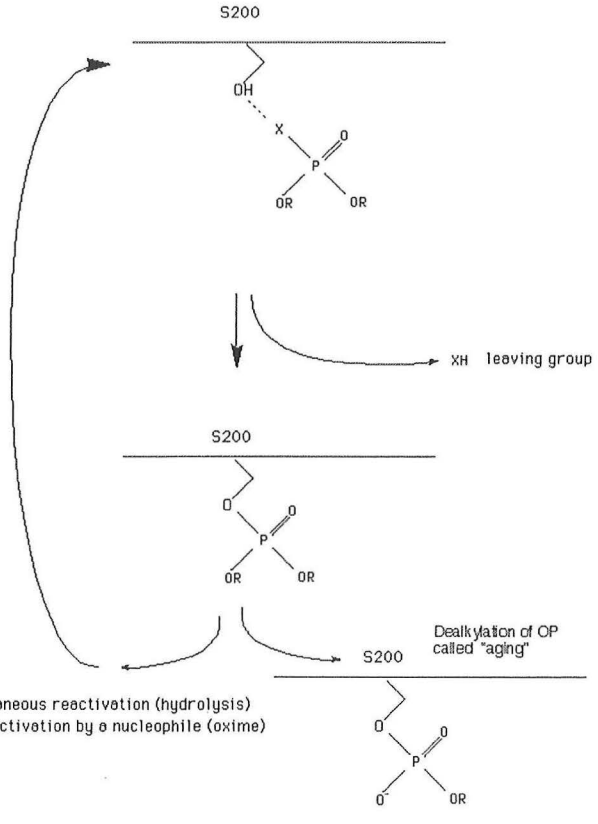


Figure 2: Metabolism of acetylcholine (*Modified after Talor P: Anticholinesterase agents. In Gilman AG, Goodman LS, Rall TW, Murad F (Eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th ed. New York, Macmillan, 1985, p 112)*

with acetyl CoA. It is catalyzed by the enzyme choline acetyltransferase, to form more acetylcholine.

Organophosphates and carbamates are attracted to this esteratic site of acetylcholinesterase, and as a result of this attraction, acetylcholine cannot enter. This precludes the cleaving of of the neurotransmitter, and causes acetylcholine excess throughout the body. Carbamates attach to both the anionic and esteratic sites. A portion of the carbamate is immediately cleaved off. The enzyme remains inactive during the time in which the carbamate remains carbamoylated to this esteratic site. This hydrolysis step may take one hour in the case of physostigmine or several hours in the case of pyridostigmine. Carbamate inactivation of acetylcholinesterase is always reversible.

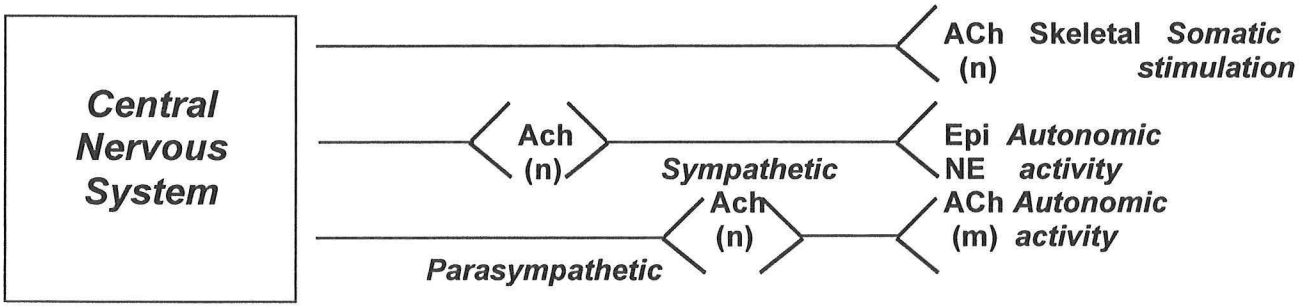
Figure 3 Organophosphate inhibition of acetylcholinesterase (ESTHER database, 19



In contrast to the carbamates, most organophosphates attach only to the esteratic site of acetylcholinesterase. Nerve agents and organophosphate insecticides combine with the hydroxyl group of a serine residue, leaving an inactive phosphorylated form of the enzyme. Depending on the size of the alkyl group on the organophosphate molecule, hydrolytic cleavage may take a long time to occur, or may not occur at all. If this bond becomes permanent, the enzyme remains inactivated definitively. New enzyme must be synthesized in order for the synapse to function normally once again. In the case of red blood cells, this period of regeneration corresponds to the life of the cell, or 120 days.

Compounds that inhibit cholinesterase are either the carbamates or organophosphates. The carbamates cause a *reversible* inhibition of the enzyme, and are used as less toxic insecticide compounds. There are several medicinal carbamates used in modern medicine. These include physostigmine, which has been in use for more than a century (Fraser TR 1863). The others are used in *myasthenia gravis*: neostigmine, pyridostigmine and edrophonium. Physostigmine is a tertiary amine. Being relatively nonpolar, it crosses the blood brain barrier and will reverse anticholinergic symptoms which are central in origin. The remaining medicinal carbamates are quaternary amines, which are charged molecules unable to cross into the central nervous system. The US and other militaries also use pyridostigmine as a pretreatment for some nerve agent exposures. The new CNS selective cholinesterase inhibitors such as tacrine or donepizel are structurally unrelated to the carbamates and organophosphates. The concept is a simple one: the carbamate occupies the active site of acetylcholinesterase enzyme in a reversible fashion. In theory, an exposure to a nerve agent would not result in binding because of this preexisting carbamate. Later, when the carbamate is released, there is no nerve agent to cause toxicity. The efficacy of this process remains controversial.

Figure 4 Acetylcholine neurotransmission



Wherever acetylcholine excess is found, there will be symptoms of cholinergic excess (figure 3: CNS, ganglionic & end organs from handout). Acetylcholine is the neurotransmitter at the neuromuscular endplate and for the parasympathetic nervous system. It is also the neurotransmitter at the ganglionic level for both the sympathetic and parasympathetic nervous systems. As a result of this, neurotransmitter excess is manifested in both the sympathetic and parasympathetic nervous system. Ganglionic, nicotinic cholinergic excess can result in tachycardia, hypertension and mydriasis which may be misleading for the clinician who expects the cholinergic (muscarinic) findings.

Signs and Symptoms of Nerve Agents and Organophosphates
Muscarinic Sites Eyes: lacrimation, miosis (often not present) Airways: bronchoconstriction, bronchorrhea, rhinorrhea Gastrointestinal: hypersalivation, nausea, vomiting, diarrhea Skin: perspiration Cardiac: bradycardia (often not seen). Nicotinic Sites Skeletal Muscles: fasiculations, weakness, flaccid paralysis Ganglionic effects: tachycardia, hypertension

Table 2 Cholinergic signs & symptoms

The cholinergic symptoms are listed in table 2. It is of special importance to include the important findings of bronchorrhea and bronchoconstriction in one's effort to remember this toxic syndrome. These are the principal causes of death in organophosphate poisoning. The resolution of pulmonary and bronchial complications constitutes the primary endpoint of treatment. The common mnemonic "SLUDGE" leaves out this very important endpoint and should not be used for teaching health care providers the characteristics of the cholinergic (muscarinic) toxic syndrome.

Laboratory testing of cholinesterases

In the blood there are two types of cholinesterases which are not identical to the tissue enzyme but provide an accessible source for measuring body cholinesterase activity. The two types are serum or butyrylcholinesterase (BuChE) and erythrocyte cholinesterase (RBC-AChE). RBC cholinesterase is generally assumed to be a more representative marker for tissue AchE activity. Agricultural workers who are occupationally exposed to organophosphates have baseline and periodic determinations of their RBC-AChE. If they have a decrease of their AChE levels they are removed from the work environment. Cholinesterase levels may vary depending on ethnicity and other genetic factors, nutritional status and underlying disease states. Considerable variation occurs between individuals.

Butyrylcholinesterase is synthesized in the liver and circulates in plasma. Its function in man is unclear. Studies that have attempted to relate symptoms of toxicity to AChE levels have found a greater correlation to RBC-AChE than to BuChE (Ketchum JS et al 1973, Grob D, Lilianthal JL Jr. 1947). Many organophosphate insecticides preferentially inhibit BuAChE, wheras nerve agents such as VX tend to inhibit RBC-AchE to a greater degree (Sidell FR & Groff WA 1974, Sim VM 1962). Once inhibited, BuAChE is re-synthesized more rapidly than RBC-AChE, the taking approximately 120 days to return to normal, or 1% per day (Grob D 1953). Bu-AChE requires approximately 50 days to return to normal levels. Butyrylcholinesterase is often referred to as serum or "pseudocholinesterase." BuAChE less than 20 percent of predicted was a useful prognostic indicator for patients for poor outcome in the Tokyo sarin terrorist attack (Okumura T 1996).

Symptoms vary in the degree that they relate to serum cholinesterase levels. Eye and airway signs are caused principally by direct exposure and have little correlation to RBC-AChE levels. (Harvey JC 1952, Craig AB et al 1959, Sidell RF 1992).

Properties of the nerve agents

The nerve agents differ in their potential toxicities (Table 2). The LCt_{50} refers to the dose that kills 50% of unprotected humans expressed as a concentration per cubic meter and with a one-minute exposure. The first three agents, tabun, sarin and soman, are considered volatile agents, with characteristics that allow their suspension in air from a properly designed dissemination device. The larger vapor density of VX is manifested by its highly viscous nature, with a consistency similar to motor oil.

Table 3 Nerve agent chemical properties (modified from Holstege CP 1997, and Sidell 1997 page 183)

Agent	Tabun (GA)	Sarin (GB)	Soman (GD)	VX
LCt_{50} Mg(min)/m3	400	100	50	10
Volatility Mg/m3 at 25 C	610	22000	3900	10.5
Vapor Density (air = 1)	5.63	4.86	6.33	9.20
Topical LD50 mg	1000	1700	100	10
Aging half-life (approx. time)	14 hours	5 hours	2-6 minutes	48 hours

Nerve agents: how they differ from organophosphate insecticides

While many similarities exist between the organophosphate insecticides (OPIs) and the nerve agents in terms of their pathophysiology and treatment, there are some differences. In cases of volatile nerve agent exposure, patients who do not present to the hospital with symptoms are not likely to become ill later. Several of the organophosohate insecticides differ in this respect. Some agents such as fenthion and chlorfenthion may cause symptoms 12 or more hours after exposure due to their strong lipophilicity. The nerve agent VX can also cause severe symptomatology much later after the exposure. Another difference with the OPIs is in the development of sequelae which occur. The chronic neuropathy associated with the OPIs does not appear to occur with the nerve agents. This is possibly due to the lack of effect on the neurotoxic esterase (NTE) by nerve agents. A difference with respect to the dosing of atropine exists between the nerve agents and the insecticides. As noted below, OPIs may require extremely large doses of atropine, whereas nerve agents rarely require more than 20-30 mg of this antimuscarinic drug.

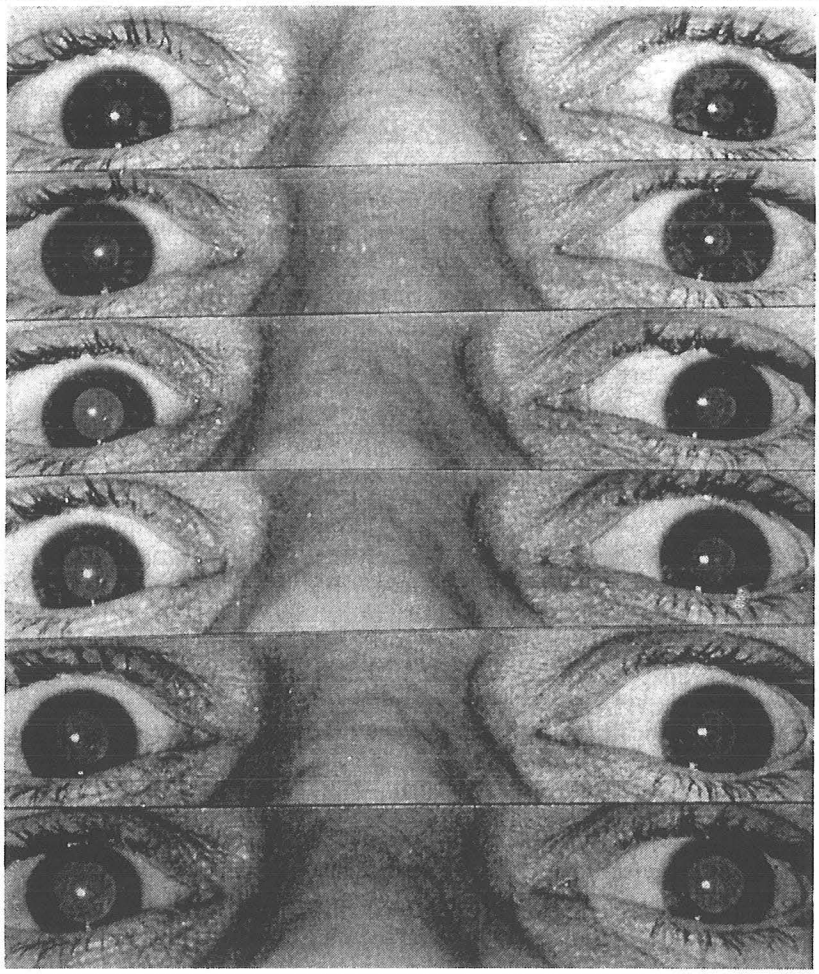


Figure 2 Prolonged miosis following accidental exposure to soman lasting 62 days (Sidell FR, 1974).

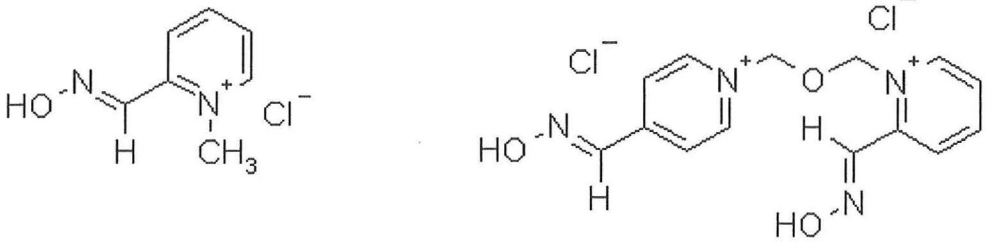
The special case of Soman

There are very few cases of soman poisoning, and to find an example of this type of poisoning, one must look back to the literature of the early 1970s. Dr. Fredrich Sidell, perhaps the best-known researcher on the chemical agents, reported a case of soman poisoning involving a laboratory worker in 1974 (Sidell FR 1974) . A 33 year old male laboratory technician was working at the Edgewood Arsenal in Maryland with one milliliter of 25 % (V/V) soman solution, broke the pipet, splashing a very small amount into an around his mouth. The account was remarkable: "He immediately washed his face and rinsed his mouth with water and was brought to the emergency room ...about 5-10 minutes after the accident. He complained of impending doom and immediately collapsed. His physical examination revealed him to be comatose with labored respirations and he was slightly cyanotic." "He had miosis (12 mm, bilaterally). Markedly injected conjunctiva, marked oral and nasal secretions, moderate trismus and nuchal

rigidity, prominent muscular fasiculations, and hyperactive deep-tendon reflexes. Except for tachycardia, his heart lungs, and abdomen were normal" (Sidell FR 1974). After a total of 12 mg of atropine and some pralidoxime, bronchoconstriction became less severe, however because of trismus he was not able to be intubated. He subsequently received a tracheostomy and awoke after about 30 minutes. Due to the atropinization and urinary distension, he required catherization to fully void. His hospital course was described as difficult with persistent fasiculations, nausea, weakness and restlessness. Although previous publications referred to worsening cholinergic symptomatology with the use of phenothiazines, he was given a dose of phenergan. He later developed torticollis that responded to diphenhydramine (Arterberry 1962 & Weiss 1967). A very remarkable feature of this case was the requirement of anticholinergic therapy for five more weeks. Scopolamine was administered with varying effects during the hospital course. The drug seemed more beneficial at the beginning, and detrimental towards the end of his medical care (Kechum et al 1973).

As with other volatile agents, miosis tends to be very predominant, and is very prolonged, as illustrated in figure 3. This fascinating series of photographs was taken by Dr.Sidell to demonstrate the long duration of miosis after soman exposure. These photographs were taken over a 62 day period where the patient was maximally dark-adapted, then a flash photograph was taken of the pupil faster than its ability to constrict.

Atropine treatment is similar to other nerve agents, exept for possibly requiring larger dosing. In the US, the only oxime reactivator available is pralidoxime. The data for 2-PAM with soman are rather unique. In an experiment utilizing rat, monkey and human muscle tissue, Clement demonstrated that 2-PAM is inefficacious in the treatment of soman poisoning. Hence, the agent used currently in the United States would not be useful for treatment of this particular poison. Other agents do appear to have efficacy, however. The lethal dose for soman is approximately 50 mg. One problem with soman is the extremely rapid aging time. Aging occurs in approximately 2 minutes, making the application of an agent such as pralidoxime essentially useless.



Pralidoxime HI-6

Figure 3 Oxime acetylcholinesterase reactivators

The bispyridinium oximes as a treatment for soman offer some promise. The structure includes an additional oxime ring: a nitrogen-substituted benzene ring with a side group. By combining oximes into larger molecules, antidotes have been developed which are effective against nerve agents. One such agent is HI-6 (see figure). Unfortunately there is not a perfect oxime reactivator which is useful for all agents. If a terrorist was informed enough, he could develop a toxin which would defeat any specific reactivator.

Hamilton investigated the efficacy of the bispyridinium agent HI-6 after giving monkeys five times an LD50 of soman. Three out of 4 monkeys survived using the newer oxime (Hamilton MG et al 1989). One of the interesting aspects of this case was the fact that acetylcholinesterase inhibition was the same for the monkeys which survived and those which died. Thus, some factor is involved in the efficacy of the bispyridinium agent other than acetylcholinesterase reactivation. Some have suggested that it is the brain cholinesterase which makes the difference in survival, however in a study involving rat brain homogenate cholinesterase activity, essentially no improvement could be found from pralidoxime in terms of enzyme reactiviation (Kassa 1999).

Diagnosis of nerve agent intoxication

Physicians are key participants in the response to a chemical agent attack. After a terrorist incident, the great majority of patients will present to hospitals without the benefit of decontamination or treatment at the scene by EMS personnel. This means that medical personnel and hospitals must plan to be able to respond to such an incident. The agents which will be discussed here include Tabun, Sarin, Soman and VX.

The primary diagnosis of exposure to nerve agents will be based on the signs and symptoms of potential victims. The majority of exposed patients will present with miosis in the case of the volatile agents. Victims of VX exposure usually do not manifest miosis. The more severely intoxicated patients will present with vomiting and seizures. Observation of these effects should provoke the inclusion of nerve agent exposure in the mind of the treating physician. The combination of miosis and muscle fasciculation is considered pathognomonic of organophosphate exposure. If several patients present with the same symptoms, this should cause the physician and hospital staff to consider the possibility of a terrorist attack with these agents. If a chemical attack occurs, one would expect that the majority of victims would arrive within a short period of time (hours) during the same day as the exposure. This differentiates a chemical terrorist attack from a biological one. In a biological attack, victims do not present until after a latent period of several days, and would likely present at hospitals all around the metropolitan area involved. Chemical agent attacks would be expected to result in many victims during a short span of time and involving only a few area hospitals.

Chemical agent confirmation using detection equipment or laboratory analysis of involved victims will take considerable time, and will not likely contribute to the early management of these mass casualty incidents. Hence, the correct

diagnosis based on signs and symptoms will be essential in the response to a terrorist incident of this nature.

Treatment of intoxication with nerve agents

Treatment of nerve agents should always follow proper decontamination of the victims (discussed below). If patients who are not properly decontaminated are brought into the hospital, many of the staff members may become secondarily contaminated and develop injury from exposure to the nerve agent involved (Nozaki et al 1995).

The acute management of the patient with nerve agent exposure involves the rapid establishment of a patent airway. The major cause of death is hypoxia resulting from pulmonary and bronchial involvement with the toxin. In cases of severe bronchoconstriction and bronchorrhea, it may be necessary to provide atropine before other interventions are attempted. Endotrachial intubation may not be successful without the application of atropine due to the extremely high airway resistance resulting from bronchoconstriction, on the order of 50-70 cm H_2O. This is higher than the pressure allowed by the "pop-off" valve of most bag-valve mask devices. Once atropine is applied and intubation is carried out, aggressive pulmonary toilet should be initiated, including frequent suctioning of secretions. Military experience indicates that these interventions can be life-saving in victims even with severe systemic symptoms such as seizures and coma.

Antidote administration

Three pharmaceutical agents are considered essential in the management of nerve agent exposure and organophosphate insecticide intoxication: atropine, pralidoxime and diazepam (or other benzodiazepines).

Atropine is an agent with both systemic and central effects to combat the effects of acetylcholine excess at muscarinic sites. Atropine dosing should begin with typical ACLS doses of 1-2 mg, but may require much more than the usual amounts after this initial test-dose. Lack of response to normal doses of atropine is a hallmark of organophosphate intoxication. Patients with severe muscarinic effects will require larger amounts of atropine. Atropine may be given by various routes including intramuscular (IM), intravenous (IV) or Endotracheal (ET). The endpoint of atropine administration is the clearing of bronchial secretions and decreasing ventilatory resistance. This is an essential point to remember, because heart rate and pupil diameter are not useful parameters for monitoring the response to treatment with this antidote. Nebulized bronchodilators such as albuterol are not as effective as atropine at treating nerve agent exposure, due to the need for an anticholinergic effect (Sidell, 1997).

Typical doses for atropine in severely intoxicated nerve agent casualties are in the range of 5-15 mg given parenterally (Sidell FR 1974, Ward JR 1962). This is in sharp contrast to the to the much larger doses required in organophosphate insecticide intoxication, in which several grams of atropine may be required in the

first days of treatment. (Vale JA et al 1990, Chew LS et al 1971). In cases of severe organophosphate poisoning an intravenous drip is implemented to meet the continuing requirement for atropinization (LeBlanc Fn et al 1986). The organophosphate insecticides may be sequestered in lipid compartments or may require a greater time for metabolism. Hence the need for prolonged treatment in many cases of poisoning by these agents.

Atropine causes the anticholinergic toxic syndrome when administered in excess of the amount required to reverse the muscarinic effects (Keyes, 1998). The anticholinergic syndrome is characterized by mydriasis, tachycardia and hypertension, urinary retention and dry skin. The blocking of perspiration may be a dangerous effect in the setting of high ambient temperatures or continued physical activity on the part of the patient. With the inability to dissipate heat, hyperthermia may ensue with resultant rhabdomyolysis and other life-threatening effects of increased corporal temperature. These patients should be monitored with a rectal probe at frequent intervals, and be kept in a cool environment.

Pralidoxime Chloride (2PAMCl)

The oximes are nucleophilic substances that reactivate the acetylcholinestrase inhibited by organophosphate toxins. They exert their effect by removing the organophosphoryl moiety. As noted in figure 3 above, the organophospate attaches to the esteratic site of the enzyme. After this, the bond may either be regenerated by an oxime antidote or it may become permanent when an alkyl group is given off. The latter process involves the production of a permanent bond, after which reactivation of AChE is no longer possible. This process is called "aging," and is related to the size of the alkyl group attached to the organophosphorus compound. Aging occurs at different time intervals from exposure for different nerve agents. For example Sarin requires several hours to age, whereas soman ages in only 2-6 minutes (table 1). VX has the longest aging time of the nerve agents, requiring greater than 2 days. The time for complete aging is about 10 times the half-life, and treatment with an oxime may be useful up to this point.

Once the oxime has regenerated acetylcholinesterase, the enzyme resumes its critical role in the breakdown of acetylcholine, normalizing neurotransmission. This will bring about the improvement of nicotinic symptoms such as fasiculations, muscle twitching, and the return to normal muscle strength. This antidote also may improve breathing, although it will not treat the muscarinic symptoms discussed previously, such as bronchorrhea and bronchoconstriction. Hence pralidoxime is always given in conjunction with atropine, and not alone in the treatment of nerve agent exposure.

Usually an exposure to sarin allows adequate time for clinicians to treat the patient if enough of the antidote is available. The exception to this is soman (GD), which has an aging time so rapid that it is impossible to administer the antidote in a realistic time frame. Nevertheless, the patient should be treated with pralidoxime in all cases where a nerve agent is suspected without consideration to the possibility of soman being the cause. The exact identity of

the agent is usually not known early in the course of the incident, and pralidoxime will not harm a soman-intoxicated patient.

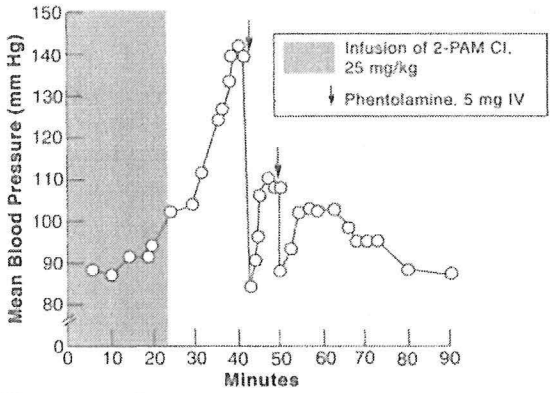


Fig. 5: Pralidoxime-induced hypertension. Sidell FR, 1997.

Pralidoxime is administered by slow IV infusion over 30 minutes. The main side-effect of rapid infusion is hypertension. This hypertension is rapidly responsive to phentolamine (Sidell FR). However it is unlikely that treatment for hypertension would be necessary in all but exceptional circumstances. The adult dose is one gram, which may be repeated every hour for a total of up to 3 grams. Dosing may be modified for administration to children.

Autoinjector administration of antidotes

The US military has produced an autoinjector which uses the same technology that most clinicians are familiar with for rapid epinephrine self-administration. The military kit, known as the MARK I consists of two autoinjector pens. The smaller autoinjector contains 2 milligrams of atropine and is administered IM. The base of the kit is held in the non-dominant hand so that the larger injector is on top and both are held at eye-level. The smaller, atropine-containing pen is removed first by holding it as a pencil. It is important to avoid holding these devices by the ends as the automated triggering device may be set off, inadvertently injecting the health care provider instead of the patient. With the other hand one checks the injection site – usually the lateral thigh – for objects which may interfere with the administration, such as coins or wallets. The atropine autoinjector is removed and the plastic-covered tip is applied as with a pencil to the injection site with a firm, even motion. The autoinjector will then "fire." It should be held in place for at least 10 seconds. Then the autoinjector is disposed of in a sharps container. After the atropine is administered, the 1-PAMCl is administered in the same fashion either to the same thigh or to the opposite side. The number of autoinjectors administered should be noted on the patient or on the victim's hospital documentation. For more exact instructions, the insert should be consulted prior to using this device.

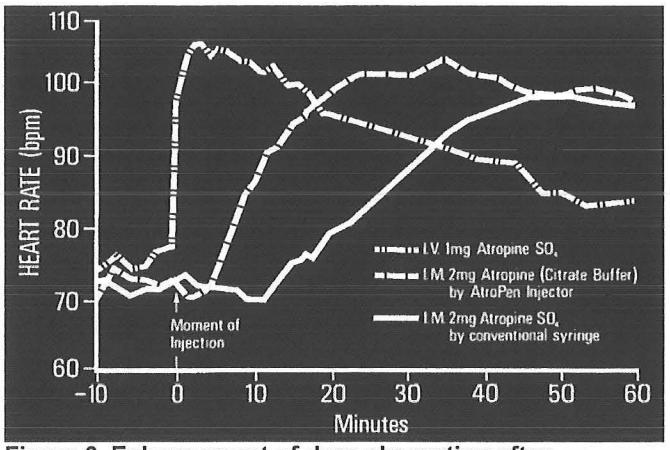


Figure 6 Enhancement of drug absorption after administration by an automatic injector (Sidell FR, Markis JE et al, 1974)

Figure 6 illustrates the efficacy of administration of pharmaceutical agents using the autoinjector device. The authors used heart rate to demonstrate the effect of atropine administration given either IV, IM or by autoinjector. The graph illustrates the effectiveness of the device. Intravenous administration causes an effect more rapidly but has a shorter duration of action. Moreover, establishment of an intravenous line may take some time in the field, and use of the kit will result in more rapid resolution of toxic symptoms. Each institution must decide on the practicality of the use of these kits in hospitals, taking into account the cost and shelf-life of the product (approximately $17.00 each with a shelf-life of 5 years – information provided by Meridian Medical Technologies).

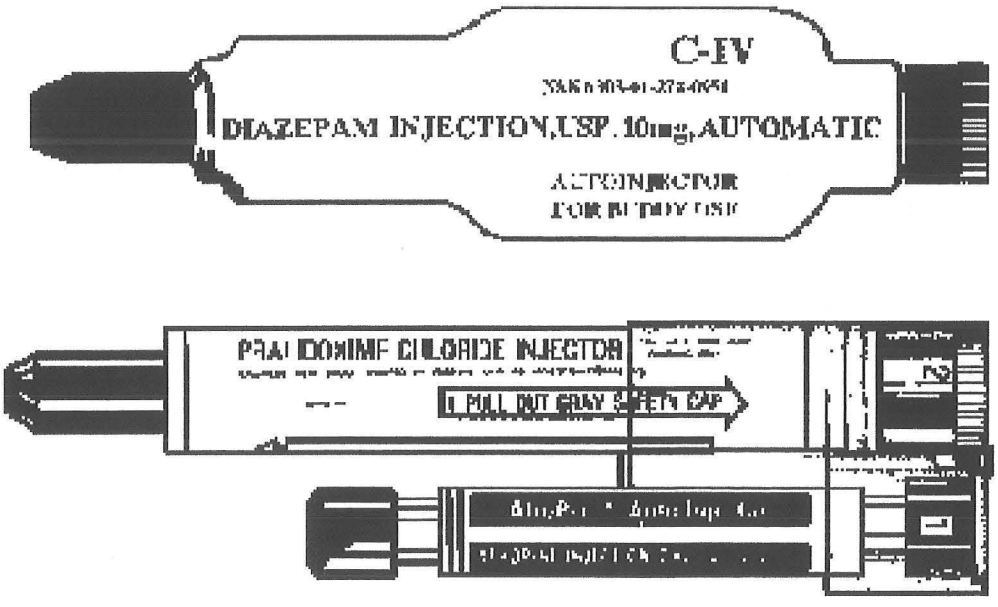


Figure 7: autoinjectors for the treatment of nerve agent exposure

The administration of atropine intravenously may be more practical in the hospital setting. It is essential for institutions to prepare for the eventuality of a large numbers of casualties. Atropine may be obtained as a powdered form, which may be compounded in the hospital pharmacy. The powdered drug has a much longer shelf life than does the atropine-containing solution. One alternative is to have enough atropine solution on hand for 30-40 casualties, and utilize the powdered form after the initial stock is completed. Compounding of atropine solution from the powdered form can be initiated in the pharmacy after the first cases arrive at the hospital.

Diazepam or other benzodiazepines should be utilized to treat the seizures induced by the nerve agents. This can be administered intravenously or through the use of an autoinjector. It is assumed that in the hospital setting intravenous administration would be most practical. Military sources suggest that in patients manifesting symptoms of severe toxicity, benzodiazepines should be administered even before seizures are evident. If three of the MARK I kits are administered (due to more severe symptomatology) diazepam should be administered immediately after completing the administration with the autoinjector kits. With the exception of benzodiazepines, conventional treatment modalities for seizures are considered ineffective in this setting, including phenytoin, (Soldier Biological and Chemical Command (SBCCOM), 1999 Domestic Preparedness Training program handbook).

Treatment of nerve agent casualties should be based on the initial signs and symptoms, and modified appropriately when the actual agent is defined. If the exposure was a volatile agent, such as sarin or soman, the patients will be symptomatic within the first hour of exposure to the toxin. This usually means that patients who are not symptomatic when they are evaluated at the hospital are not likely to become serious exposure victims. For the case of the liquid exposure of VX, patients may not become symptomatic for up to 18 hour, and so should be observed for a much longer period of time. If the exposure history is not certain, it is prudent to institute the longer observation period for these patients. The degree of symptomatology will determine the dose of the antidotal therapy (see table 4)

Table 4: Nerve Agent Treatment			
Mild vapor or liquid exposure	Miosis only	Observation with no initial treatment	
Mild vapor exposure	Miosis, nasal congestion with mild shortness of breath	One mark I kit or 2 mg atropine, 1 gm 2PAMCl	Miosis may not reverse with treatment.
Mild liquid exposure	Localized sweating and fasiculations	One mark I kit or 2 mg atropine, 1 gm 2PAMCl	
Moderate Vapor or liquid exposure	More severe respiratory distress, muscular weakness	One or two mark I kits or 2-4 mg atropine, 1 gm 2PAMCl IV drip over 30 minutes	
Severe vapor or liquid exposure	Unconscious, possibly seizing or flaccid, possibly apneic or severe Sxs.	3 MARK I kits or 6 mg atropine and 1 gram 2-PAMCl initially	May repeat atropine as needed and 2-PAMCl in one hour

Personal protective equipment (PPE)

Personal Protective Equipment (PPE) refers to special garments designed to protect the members of the decontamination team against exposure to the toxic materials. The components of PPE include suits, eye protection, boots, gloves and respiratory devices. There are various types of PPE available depending on the agent involved and the risk of exposure. Not all hospital staff members require sophisticated PPE provided that victims are adequately decontaminated prior to entering the hospital. All personnel who work with decontaminated patients should work in a well-ventilated environment and utilize basic universal precautions including the use of a facemask. Universal precautions do not prevent the inhalation of a nerve agent, however they do minimize the risk of secondary contamination from splash and small amounts of contaminants that might not be removed from the victim.

The use of more sophisticated PPE is required by any personnel who will be involved in decontamination and also for those involved with the initial triage of victims. Those who use this type of equipment are required to receive appropriate training as mandated by OSHA (29 CFR 1910.120 and 19410.134), and also in some cases by NIOSH, EPA and JCAHO.

Three levels of PPE are typically described. Level A is the most sophisticated, fully encapsulated type of equipment, often referred to as "moon suits." These suits are useful primarily at the scene of agent release (Immediately Dangerous to Life and Health – IDLH). This level of protection is resistant to penetration by liquids or vapor and requires SCBA – self-contained breathing apparatus. This level of protection is difficult to wear for long periods of time due to the heat and claustrophobia engendered. In a warm setting such as the southwestern US this type of PPE is often limited to short periods of use.

Level B PPE utilizes SCBA or a supplied air respirator (SAR), but it provides a lesser degree of skin protection. This level of protection is adequate for vapor agents, and is the choice of many hospitals for the decontamination team who will be the front-line with arriving victims. The SCBA provides a positive-pressure to allow for outward flow of air, and protection against inhalation of the toxic agent.

Level C PPE makes use of air-purifying respirators where the identity of the agent is known in advance. Ideally the concentrations should also be known and determined to be below a hazardous level. The respirators include canisters, which filter the contaminated air and remove toxicants. Two basic types exist: a positive-pressure-powered air-purifying respirator (PAPR) has a battery-operated fan, which maintains airflow through a filter then, into the mask chamber. A negative-pressure respirator requires that the air be pulled across a filter by the user's own inhalation-induced vacuum. Canisters for level C are being produced with a greater spectrum of protection. Some institutions are considering level C PPE for their decontamination team on the basis of these new developments.

For any level of PPE selected, individuals will require training and a screening physical examination prior to their actual use. Training in the use of PPE and in decontamination techniques allows greater confidence and safer use of the equipment. It is also important to rotate staff to avoid fatigue and heat injury. Specific medical records should be maintained for staff members involved in the decontamination team.

Decontamination of nerve agent and organophosphate insecticide exposure

Decontamination is the process of physically removing toxic substances from a victim, equipment or supplies. In the hospital setting, it is imperative to avoid the introduction of contaminated elements into the clinical setting. In most cases, the victims will arrive at the hospital nearest to the incident with no prior decontamination. Institutions should have a plan for decontaminating victims of HAZMAT incidents including those involving terrorist nerve agents, a training program for the personnel involved in decontamination and a plan for protecting

the city water supply against contamination with toxic runoff. All personnel involved in decontamination should have PPE. In the terrorist sarin incident in Tokyo, many hospital personnel were secondarily contaminated due to their involvement in removing clothing or working in poorly ventilated environments. At one such institution, the Keio University School of Medicine, 13 developed symptoms of secondary contamination from off gassing of the nerve agent (Nozaki H et al 1995).

For the volatile agents such as sarin, the decontamination is nearly complete with the simple removal of clothing and jewelry by the decontamination team. Use of large amounts of low-pressure water will adequately complete the decontamination along with the use of soap and a gentle brush to assist in the removal of fat-soluble substances. Decontamination is most ideally undertaken outdoors near the hospital emergency department. This outdoor setting is especially suitable for areas of the US with milder weather. Indoor facilities are necessary in conditions of severe Winter weather. Security personnel should have a plan to direct traffic to this area, and to prevent entry of persons into other parts of the hospital. Signs, the presence of security personnel and locking access points will help to assure the proper flow of traffic.

Bleach solutions have been advocated for use in decontaminating victims of chemical agents. While there may be some benefit to the use in certain circumstances, for example immediately after a mustard exposure, it is not necessary for this to be done to living victims in the setting of a nerve agent exposure. Cadavers exposed to nerve agents may require special hypochlorite treatment, however. Simple soap and water is adequate for other circumstances. In a large-scale exposure such as the sarin attack in Tokyo -- where more than 600 patients arrived within the first hours after the incident -- concern over use of hypochlorite would be inappropriate. The simple removal of clothing and jewelry outside of the facility by properly protected decontamination personnel would have essentially eliminated the secondary contamination problems they experienced in the Tokyo incident.

All aspects of response to a terrorist multiple casualty incident (MCI) should be incorporated into drills. An incident command structure should be implemented to allow an organized response from all elements of the hospital community.

Conclusion

Chemical terrorist weapons are an important threat as we enter the new millenium. Considerable financial investment is being made by the United States government to prepare the civilian health sector for such an eventuality. Experience has shown that the EMS health care sector will not be handling the majority of the victims of terrorism. It is therefore incumbent upon members of the hospital staff to prepare for their direct presentation to our doorstep. The victims of chemical terrorism will arrive in large numbers, at an unexpected time, and will be contaminated with lethal nerve agent. These patients will be in need of decontamination, triage and definitive treatment as a result of their exposure.

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