18 Chemical Warfare: A Brief History and Summary of Current Threats and Initial Management

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18.1 Introduction: Tokyo, 1995

On March 20, 1995 at 8:09 a.m. the Tokyo Metropolitan Fire Department (TMFD) received an emergency call from a Tokyo subway station. Within 1 h, there were calls from 15 different subway stations with similar reports, symptoms ranging from mild visual complaints to cardiopulmonary arrest. The incoming information rapidly overwhelmed the communication abilities of the ambulance control center. During the incident, 1364 EMTs and 131 ambulances were dispatched. A total of 688 patients were transported by TMFD in ambulances or minivans and more than 4000 additional patients arrived at hospitals in the area either on foot, in taxis, or in personal vehicles.

It took several hours to appreciate that incident was initiated by members of a religious cult who had deposited bags of liquid sarin in five subway cars. Sarin is a potent nerve agent that acts by inhibiting the enzyme acetylcholinesterase, leading to a cholinergic toxidrome. Its effects are immediate and life threatening. The sarin began to vaporize once the bags were opened. This resulted in immediate symptoms in the passengers who then hurriedly exited the cars all the while allowing the gas to continue to disperse. Communications between the police department, EMS, and hospitals were overwhelmed. The police department confirmed 3 h after the incident that the substance was sarin, not acetonitrile as originally reported. The staff at the treating hospitals only became aware of the nature of the exposure after it was reported on the news [1].

The most severe cases were transported immediately, but due to laws in place in Tokyo EMS personnel were unable to perform rescue airway procedures or even place IVs without consent from a physician. As they had lost contact with the control center, no communication with the physician was available and no rescue airways were performed in the field. Only one IV was placed prior to a patient arriving at the hospital.

St. Luke's Hospital received a report at 8:16 a.m. that a gas explosion had occurred at a subway station. Hospital staff began preparation to care for expected burns and carbon monoxide poisonings. The first patient arrived on foot at 8:28 complaining of eye pain and visual disturbance. Within the first hour over 500 patients were received at the St. Luke's

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emergency department, including three patients in cardiopulmonary arrest.

Once the agent was known to be sarin, hospital staff began administering appropriate and focused antidotal therapy (i.e., atropine and pralidoxime (2-PAM)). Severe cases of organophosphate poisoning may require extremely high atropine dosing, on the order of several hundred milligrams. In storage, St. Lukes had 100 ampules of 2-PAM, each containing 500 mg, and 1030 ampules of atropine sulfate, each containing 0.5 mg. At early stages, orders were made for more medications. In total, 700 ampules of 2-PAM and 2800 ampules of atropine sulfate were used [2].

As a result of this attack, 12 were killed and over 5500 sought medical care. Of 1364 EMTs, 135 showed symptoms of secondary exposure. At St Luke's Hospital, 23 % of the staff surveyed after the incident reported symptoms of secondary exposure. Throughout the incident, only standard personal protective equipment, limited mostly to gloves, was worn by EMS and hospital staff.

Although this attack was a peacetime event, it illustrates how easily a chemical weapon attack can in any setting overwhelm any medical or disaster response system. There is much to be learned from such an uncommon, large-scale local event, both nationally in Japan and internationally [3]. A chemical weapons attack differs from usual warfare tactics or large-scale attacks in that decontamination and prophylaxis play a large role in limiting casualties [4]. It is vital for every physician or provider to be familiar with the possibilities of chemical warfare, the presentations of key agents, and the interventions necessary to save lives.

18.2 History of Chemical Warfare

Chemical weapons have been part of warfare for as long has history has been recorded. A chemical weapon can be defined as any chemical agent that is designed to seriously injure, kill, or incapacitate opposing forces. Throughout history this has taken many forms and the acceptance of such methods of warfare has undergone numerous and sophisticated evolutions.

Early chemical weapon use included poison darts and arrows that utilized the natural venom extracted from scorpions, snakes, and frogs. The Laws of Manu, a Hindu text circa 500BC, was against the use of poison arrows and darts as part of warfare, but advocated the use of poisons in the enemy's water and food. Ancient Chinese texts describe the use of arsenical smoke to incapacitate the enemy. In ancient Greece, various plants were used as weapons to poison the enemy. In the Siege of Kirrha, a battle that took place during the First Sacred War in 590BC, hellebore was used to poison the aqueducts of Kirrha, causing severe, incapacitating diarrhea in the city's inhabitants [5].

In the early modern era, use of chemical weapons continued to evolve. Leonardo da Vinci advised throwing chalk, arsenic, or powdered verdigris on enemy ships to cause asphyxiation. In 1675 the Strasburg agreement, the first international agreement to ban the use of poison projectiles, was signed by France and Germany in response to the use of belladonna alkaloids during the siege of Groningen, part of the Franco-Dutch War [5].

Moving forward, the use of chemical weapons continued to be controversial. In 1894, during the Siege of Sevastopol, a British chemist by the name of Lyon Playfair advised the use of cacodyl cyanide artillery shells against enemy ships to solve a stalemate. The Admiral of the Royal Navy backed the idea, but the British Ordinance Department rejected the proposal on ethical grounds. Lyon Playfair's response was that the use of chemical weapons is no different from other forms of warfare; and this defense was used well into the twentieth century to justify their use [5].

More modern forms of chemical warfare came into play in World War I, also called the Chemist's War. The first notable use was in Yper, Belgium. On April 22, 1915, the Germans released 160 tons of chlorine gas over the French and Algerian military, killing over 1000 soldiers and injuring over 4000 more. Yper became a testing ground for German chemical weapons. Mustard gas was introduced later in the war, often nick-named

"yperite" and within 6 weeks of introduction was responsible for 20,000 casualties [6].

While the use of chemical weapons in WWI was limited to Germany, the development of these technologies was not. Within 1 year of the United States entering the war on April 16, 1917, Johns Hopkins, Harvard, and Yale all had programs dedicated to the development of chemical weapons as well as initiating preventive measures including more advanced gas masks and antidotal treatments. The French also had several medical schools and universities with chemical weapon programs [6].

World War II saw further development of chemical weapons from Germany, with the first nerve agents developed from chemicals previously intended to be pesticides. While several countries, Allied and Axis alike, had stockpiles of chemical weapons, there are no documented incidences of chemical weapons use in combat during WWII, although the constant threat of use in combat loomed over both sides for the duration of the war [6].

Since WWI, chemical weapons have remained a threat both during wartime and peacetime. In the Iran–Iraq war in the 1980s, 5 % of Iranian casualties were due to chemical weapons, again drawing attention to the threat [6]. During the Cold War, the stockpiles held by the US and the Soviet Union totaled tens of thousands of tons, enough to destroy most of life on earth.

International ongoing efforts to both identify and destroy stockpiles of chemical weapons have had some success, however, until there is 100 % cooperation internationally, the possibility of chemical attack remains a real one. The remainder of this chapter will cover the individual presentations, prophylaxis, decontamination, and treatment for individual chemical agents.

18.3 Agents: Presentation and Management

18.3.1 Asphyxiants

An asphyxiant is any substance that prevents the body from utilizing oxygen. Two categories include simple asphyxiants like carbon dioxide and nitrogen, and systemic asphyxiants such as cyanide. Cyanide is the most notorious asphyxiant relevant to chemical warfare. Although little research exists focusing on mass exposures to cyanide, there are some case reports and small series available on cyanide toxicity primarily through exposures in civilian settings from burning synthetic materials. These data, in addition to several animal studies, are our best resource for determining best treatment for cyanide if used as a chemical weapon.

In civilian settings, cyanide toxicity is usually diagnosed through a combination of historical and physical examination findings. Patients have generally been exposed to an explosion or fire in which synthetic materials were burned. They will often present with concomitant burns or even carbon monoxide poisoning, complicating the clinical picture. These confounding factors may or may not be present in an intentional chemical attack, so high clinical suspicion will be paramount to proper treatment [7, 8].

As cyanide exerts its effects through inhalation or GI tract absorption, superficial decontamination and secondary exposure do not play a large role. Effective prophylaxis may be limited to on-scene rescuers wearing proper protective clothing, however, given that the identity of the gas or toxin involved may not be known at the time, rescuers and those assisting in the area should be instructed to don full gas mask and protective Mission-Oriented Protective Posture (MOPP) gear. The potential for release of more than one toxin in any attack also warrants this precaution.

Patients exposed to cyanide will exhibit a host of vague symptoms including but not limited to anxiety, altered mental status, shortness of breath, tachycardia, bradycardia, hypotension, hypertension, nausea, vomiting, dizziness, headache, seizures, and coma [7, 8]. Classically it is described as having a bitter almond odor, but this may not always be present and a significant percentage of people are genetically unable to detect this odor. The variability of symptoms again makes the diagnosis difficult. Cyanide levels in the blood take too long to obtain to be useful in the initial evaluation and treatment. If cyanide is suspected, a lactate level is recommended to help

determine likelihood of cyanide toxicity. Studies have shown a lactate level of >10 mmol/L is consistent with cyanide toxicity in patients with less than 15 % body surface area burns [8]. If not already started, this may prompt clinicians to initiate antidotal treatment for cyanide when the history and clinical picture fit the possibility.

At the cellular level, cyanide is a potent noncompetitive inhibitor of cytochrome c oxidase, leading to cellular hypoxia and tissue death. Cyanide is metabolized by the enzyme rhodanase to thiocyanate. Rhodanase requires thiosulfate as a substrate. Treatments for suspected cyanide toxicity work in one of three ways: (1) by binding cyanide, (2) by generating methemoglobin, which then binds cyanide, or (3) by increasing metabolism of cyanide via addition of substrate.

Today, there are several commercially available antidotes for cyanide. Hydroxycobalamin, if available, is the preferred method of treatment for cyanide toxicity [7, 8]. Hydroxycobalamin is a potent competitive binder of cyanide and binds both free and cytochrome bound cyanide, forming cyanocobalamin, which is then easily excreted by the kidneys. The efficacy of hydroxycobalamin in treating cyanide toxicity has been shown in multiple animal studies [7–10]. Studies in humans have been very limited. Several case series and case reports showed positive results. The usual dosing of hydroxycobalamin is 5 g IV over 15 min (see Table 18.1) [8].

The longest standing antidote for cyanide is the Lilly Cyanide Antidote Kit, or Lilly kit. The Lilly kit is comprised of amyl nitrite, which is inhaled, followed by IV sodium nitrite and IV sodium thiosulfate. The nitrites form methemoglobin, which then binds cyanide. The sodium thiosulfate provides substrate for rhodanase to then metabolize cyanide to thiocyanate. While the goal of using nitrites is the production of methemoglobin, this may compromise oxygen transport and become problematic in patients from fires with smoke inhalation and/or carbon monoxide poisoning which further exacerbate functional anemia and cellular shock (see Table 18.1) [11].

Other available treatments include 4-DMAP, available commercially in Germany. 4-DMAP also induces methemoglobinemia at unpredictable levels. In France and Great Britain, dicobalt edetate is approved for use. It forms a complex with cyanide that can be excreted in the urine, but has potential for cardiac toxicity, seizures, and anaphylaxis (see Table 18.1) [7, 8].

Hydroxycobalamin remains likely the safest treatment for cyanide toxicity and has shown efficacy in animal trials. Potential side effects are limited to transient hypertension, bradycardia, skin and urine color changes, and headache. When available it is the preferred treatment and has the added benefit of low risk if used by prehospital personnel [7, 10]. If known threats of chemical weapon attacks exist, a pre-hospital protocol for use of hydroxycobalamin and protocols for sufficient storage of antidote should be in place [11].

18.3.2 Vesicants

Vesicants are chemical agents that cause blistering of skin and mucous membranes. The most commonly used vesicant in war is sulfur mustard (mustard gas).

Sulfur mustard, bis-2-chloroethyl sulfide, smells faintly of mustard when released. Initially mustard gas causes no symptoms, but within 4–12 h causes eye pain, blurred vision and increased lacrimation and potentially temporary blindness, which can last up to 1–2 weeks. Patients may also develop diffuse skin redness and itching followed by edema. Typically, blisters do not develop for several days, but then form in random crops. The skin findings can be very similar to thermal burns, but often are slower healing and are prone to infection. Very high doses of mustard gas can be acutely fatal within an hour [12, 13].

Pulmonary effects of mustard gas can also be severe. Pulmonary injury is the most likely cause of death for patients exposed to mustard gas. Early signs are limited to dry cough and hoarseness. Later, sloughing of tissue and necrosis lead to obstructive symptoms. Patients are at high risk for pulmonary infections as well as ARDS. More frequent than initial symptoms, mustard gas can also lead to chronic obstructive pulmonary dis-

Table 18.1 Cyanide antidotes

Cyanide antidotes	Mechanism of action	Dosing	Side effects
Hydroxycobalamin First-line treatment Safe for pre-hospital use	Binds cyanide to form cyanocobalamin	5 g IV over 15 min Additional doses of up to 10 g may be given if needed	Transient hypertension Bradycardia Headache Skin and urine discoloration
Lilly Cyanide Antidote Kit Not preferred used if hydroxycobalamin unavailable 1. Amyl nitrite 2. Sodium nitrite 3. Sodium thiosulfate	Nitrites form methemoglobin, which preferentially binds cyanide Sodium thiosulfate provides substrate for normal metabolism of cyanide	1. Amyl nitrite 0.3 mL ampoules to be administered by mechanical ventilation or by crushing and inhaling 2. Sodium nitrite 300 mg IV over 5–15 min, additional dose up to 150 mg if needed. For peds 0.33 mL/kg of 10 % solution 3. Sodium thiosulfate 12.5 g IV over 10 min. For peds 1.65 mL/kg of	Reduced oxygen carrying capacity in blood via methemoglobin formation Vasodilation Hypotension
4-DMAP available some countries, not in US	Forms methemoglobin which preferentially binds cyanide	250 mg IV over 1 min	Reduction in oxygen carrying capacity in blood via methemoglobin formation
Dicobalt edetate Due to side effects, not recommended unless other treatments unavailable		300 mg IV over 1 min	Anaphylaxis, hypotension, arrhythmias

Sources: (1) MacLennan L, Moiemen N. Management of cyanide toxicity in patients with burns. Burns. 2015; 41:18–24. (2) Eckstein M. Enhancing public health preparedness for a terrorist attack involving cyanide. J Emerg Med. 2008;35(1):59–65. (3) Rodgers GC, Condurache CT. Antidotes and treatments for chemical warfare/terrorism agents: an evidence based review. Clin Pharm Therapeut. 2010;88(3):318–27

ease as well as chronic bronchiectasis, bronchiolitis obliterans, chronic cough, nasal mucosal abnormalities, and many other long-term respiratory issues [12, 13].

Research concerning treatment of sulfur mustard exposure has not yielded a clear antidote. Studies are limited to animals as no human studies have been conducted to date. Limited animal data have suggested that thiosulfate and *N-acetyl-l* -cysteine may have some benefit, but without verification from human studies, these cannot be routinely recommended at this time [7].

As there are no known antidotes to sulfur mustard, initial management of mustard gas exposure focuses on decontamination. The window for effective decontamination is very short. Most benefit will be derived from immediate decontamination in the field. For eye exposures, decontamination likely needs to be done within minutes in order to confer any benefit. In order to prevent further spread of the substance, which remains on the skin, patients should be decontaminated on arrival to the hospital, prior to entering any building or hospital structure. Staff should be fully attired in MOPP gear or other approved protective suits as well as a gas mask [12].

The method of decontamination is still an area of uncertainty. Recommendations in the past have included simple soap and water, various oils, and even household bleach, but no studies

have been done in humans to evaluate these methods. Limited animal studies have been done showing some benefit of iodine application to exposed areas, but there is not strong enough evidence to recommend one agent over another. Given availability, simple soap and water may be the easiest method for skin decontamination. A simple and thorough saline flush is reasonable for eye decontamination [5, 7].

Following decontamination, management becomes primarily supportive. Eye injuries may be mild or severe. Some studies in rabbits have shown small benefit to topical anti-inflammatory drugs, but there are no comparative studies in humans [7]. Consultation with an ophthalmologist, when available, is recommended.

Treatment of skin injuries is also supportive. Generally, treatment will mirror that of thermal burns with focus on preventing infection. Topical iodine and sodium hypochlorite have been studied in animals with some evidence of benefit, but again no human studies have been done [7]. Recommendations currently are to focus on immediate decontamination to prevent worsening of symptoms, then treat supportively as you would thermal burns.

There is no specific treatment for lung injury in mustard gas exposure. Some animal studies have shown benefit from steroids and from antibiotics, but no human data are available [7, 12]. While in vitro experiments have demonstrated both NAC and doxycycline to result in decreased cellular injury, these data are not robust enough to routinely recommend. Management should focus on aggressive supportive care [14].

Lewisite was a successor to sulfur mustard. It is more volatile and causes almost immediate eye irritation as opposed to the delayed symptoms caused by mustard gas. Lewisite is an organic arsenical compound and has significant vesicant and systemic toxicity [7, 12].

As with mustard gas, decontamination is important. Recommendations for eye and skin decontamination as well as for pulmonary injury are the same as those for mustard gas victims. No specific studies have been done [7]. Treatment for Lewisite exposure is simplified by availability of several antidotes.

During World War II, the British developed an antidote to Lewisite called British anti-Lewisite (BAL) [15]. Fifty-six million tubes of BAL ointment were distributed to US troops during the war [16]. BAL has also been used in civilian medicine to treat multiple heavy metal toxicities. BAL forms a complex with arsenic and was extensively tested in humans during WWII, but these data were not published. Although ointments were distributed during WWII, currently only IM administration of BAL is approved. The commercial preparation is 10 % BAL in peanut oil. Recommended dose is 0.5 mL/25 lb bodyweight up to a maximum of 4.0 mL. This dose can be repeated in 4, 8, and 12 h (see Table 18.2) [16].

BAL does have significant toxicity, resulting in persistently rising systolic and diastolic blood pressures, tachycardia, headaches, nausea, vomiting, anxiety, sweating, and even coma and convulsions at high doses [15]. Newer antidotes to Lewisite are 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-dimercaptosuccinnic acid (DMSA), two water-soluble analogs of BAL. DMSA and DMPS are both less toxic than BAL and can be administered orally. There are no routinely recommended dosages for Lewisite exposure as there has been no opportunity to use these drugs in humans exposed to Lewisite. Animals studies show positive results in rabbits exposed to Lewisite who are then treated with DMSA or DMPS up to 90 min post exposure (see Table 18.2) [7, 15].

Treatment of Lewisite should focus on administration of appropriate antidotes. BAL, DMSA, and DMPS have all been shown to benefit patients. DMSA and DMPS have a better safety profile than BAL, but choice of agent will likely depend on availability.

18.3.3 Pulmonary Irritants

Pulmonary irritants are agents that cause lung irritation by penetration into the tissues of the airways. Chlorine and phosgene are the two pulmonary irritants that have been used most frequently in warfare. Both agents act by forming hydrochloric acid on contact with water, causing airway

Table 18.2 Lewisite antidotes

Lewisite antidotes	Mechanism of action	Dosing	Side effects
British anti-Lewisite (BAL) (dimercaprol) [a]contraindicated in renal disease, pregnancy, concurrent use of medicinal iron, and peanut allergy	Chelates arsenic	3–5 mg/kg deep IM injection q4hr for 4 doses, then repeated as needed depending on severity	Usually seen at 5 mg/kg dose: Vomiting, seizures, stupor, coma, headache, anxiety, chest, and throat pain
DMSA (meso-2,3-dimercaptosuccinic acid)	Chelates arsenic	10–30 mg/kg/day in three divided doses (3 days on, 11 days off, for 8 cycles)[a]	Uncommon: GI disturbances, urticaria
DMPS	Chelates arsenic	3–5 mg/kg IV over 5 min q4hr for 24 h, then 400 mg PO q4hr for 1–5 days	Hypotension, allergic reaction, skin rashes

Sources: (1) Agency for toxic substances and disease registry [Internet]. Atlanta: Centers for Disease Control; 2014 [cited 2015 Jun 7]. http://www.atsdr.cdc.gov/mmg/mmg.asp?id=922&tid=190. (2) Alternative Medicine Review. Monograph: meso-2-3-dimercaptosuccinic Acid. [Internet] [place unknown] Thorne Research, Inc; 2001 [cited 2015 Jun 7]. http://www.altmedrev.com/publications/5/3/264.pdf. (3) Ronco C, Bellomo R, Kellum J. Critical Care Nephrology. Elsevier Health Sciences; 2008. (4) Moore DF, O'Callaghan CA, Berlyne G, Ogg CS, Davies HA, House IM, et al. Acute arsenic poisoning: absence of polyneuropathy after treatment with 2,3-dimercaptopropanesulphonate (DMPS). J Neurol Neurosurg Psychiatr. 1994;57:1133–35

[a]*Note:* dosing of DMSA and DMPS based on doses for general heavy metal chelation, not specific to Lewisite exposure

tissue edema and capillary leakage [7]. Chlorine also produces hypochloric acid and an oxygen-free radical on contact with water, all contributing to lung damage [17].

In addition to formation of hydrochloric acid, phosgene also undergoes acylation, a reaction by which phosgene loses carbon and oxygen atoms to nucleophilic components in the tissues, causing direct damage to lung surfactant followed by downstream release of arachadonic acid mediators. Ultimately, this leads to vascular permeability, alveolar leakage, and pulmonary edema [18].

Chlorine is easily obtained and easily dispersed and has a relatively higher water solubility than phosgene. This property results in more immediate noxious effects resulting in victims fleeing the site of exposure and not allowing lower airway effects to occur. However, exposure to large doses may in fact penetrate lower airways [17]. Chlorine may also have effects on the eyes and skin, although these are easily treated with water or saline flushes [7]. Chlorine acts much more rapidly than phosgene, causing symptoms within minutes. If symptomatic, patients usually present with cough, hemoptysis, chest tightness, and dyspnea [14].

Phosgene, in high enough concentrations, smells of musty hay or green corn. Initial exposure to phosgene can cause some mild eye irritation via formation of hydrochloric acid. As with chlorine, simple eye washes and irrigation are effective in treating these symptoms. Phosgene's property of lower water solubility allows victims to have ongoing exposure without immediate upper airway effects. Therefore, the lower airways are more affected than in chlorine gas exposures. After high concentration exposure, immediate symptoms may include throat irritation, cough, headache, nausea, vomiting, and chest tightness. It is important to emphasize that delayed symptoms may not appear for up to 48 h and patients may be symptom free for this period. Later symptoms are secondary to acylation as opposed to hydrochloric acid formation. Delayed symptoms include cough, dyspnea, tachypnea, and respiratory distress caused by pulmonary edema [14, 18].

There are no antidotes to chlorine or phosgene and there is some controversy concerning treatment for lung injury. Management is primarily supportive with positive pressure ventilation and humidified oxygen. Limited animal and human

series support this approach, but no controlled studies in humans have been done [7]. Bronchodilators can be given if bronchospasm develops, but otherwise are not routinely recommended [7, 14].

There are some animal studies and case studies supporting the use of nebulized sodium bicarbonate in chlorine inhalation with some improvement in respiratory function. One prospective study in humans exposed to chlorine showed some improvement in FEV1 and quality of life after nebulized sodium bicarbonate, but otherwise no significant difference was found [7, 17]. In animals, *N*-acetyl-L-cysteine has shown some benefit in decreasing lung pathology after phosgene exposure [14, 18]. Corticosteroids may be of some benefit in both phosgene and chlorine exposure based on success in other inflammatory lung conditions as well as animal studies, but again no human studies exist to confirm this benefit so this cannot be routinely recommended [17, 18].

In summary, care of patients exposed to pulmonary irritants depends on awareness of the likely areas of injury. If a report of chlorine or phosgene attack is given, on-scene providers must decontaminate when possible and use protective gear. In a hospital setting, providers must anticipate need for respiratory support for a large number of patients, initial care likely being limited to humidified oxygen and positive pressure ventilation if indicated.

18.3.4 Nerve Agents

Nerve agents as a group are potent derivatives of organophosphate pesticides. The most notable weaponized forms of organophosphates currently in existence are tabun (GA), sarin (GB), soman (GD), and VX, although there are many others [7]. Nerve agents are colorless, odorless, tasteless, and do not cause skin irritation. They can be dispersed and are harmful as vapor, liquid, or aerosol. Much of the research concerning organophosphates is limited to commercial exposure from pesticides. It is uncertain if these data can be safely extrapolated to include treatment of nerve agents, but it is currently the best information available [7, 15, 19, 20].

Nerve agents are irreversible inhibitors of cholinesterase enzymes, primarily acetylcholinesterase (AChE). AChE is an enzyme responsible for breaking down acetylcholine (ACh), the neurotransmitter that acts at post-synaptic nicotinic and muscarinic receptors. By inhibiting the breakdown of ACh, nerve agents act to increase activation at these receptors, leading to a cholinergic toxidrome. The relative potency of these agents depends on the time it takes for the bond between the agent and the enzyme to "age," or become an irreversibly inactivated enzyme. While soman ages within minutes, sarin and tabun take hours and VX even days [7, 20].

Symptoms of the cholinergic toxidrome begin immediately. Increased ACh at muscarinic receptors causes miosis, bradycardia, increased airway secretions, vomiting and diarrhea, hypersalivation, and increased urination. ACh at nicotinic receptors causes pupil dilation, tachycardia, bronchodilation, hypertension, sweating, and muscle weakness. At central receptors, increased ACh causes anxiety, confusion, lethargy, coma, and seizures. The overall picture can vary greatly. Significant exposures can cause death within minutes. Mortality is commonly attributed to excessive secretions resulting in pulmonary edema, hypoxia, and ultimately respiratory arrest [15].

Patients are exposed through inhalation or absorption through skin. As with all agents so far discussed, decontamination is extremely important. Emergency personnel should don full protective gear and gas mask. All clothing should be removed from the patient. Simple soap and water, or water alone is likely sufficient to remove residual agent, however this will not break down the agent, so disposal of runoff must be managed so that agent does not reach general water supply or sewer system [7, 15]. There are some formulations for decontamination available through the military that are composed of charcoal or adsorbent resins, but no studies have compared efficacy of these various decontaminants. If they are available,

they should be used [15]. Decontamination must occur as soon as possible and prior to patient entering a treatment facility.

Standard antidotes available for treatment of nerve agent exposure are atropine and pralidoxime (2-PAM), with benzodiazepines as needed for seizure activity. Atropine competes with excess acetylcholine by binding and inactivating muscarinic acetylcholine receptors, therefore acting as an antimuscarinic agent [20]. Atropine counters bronchoconstriction and secretions as well as nausea, vomiting, and diarrhea. Atropine also partially counteracts the central respiratory depression caused by nerve agents [15]. Since increased respiratory secretions and respiratory depression are the main cause of death, atropine is the most important initial treatment.

Dosing of atropine will vary according to the severity of exposure. The US military provides Mark 1 kits with autoinjectors of atropine, each containing 2 mg. In minor cases, one injection may suffice, but repeated doses may be needed in more severe cases. Generally, atropine should be initiated intramuscularly or intravenously as soon as possible. Initial dose may range from 2 to 8 mg depending on severity of symptoms. Patients should be re-dosed with atropine every 3–8 min as long as symptoms persist. Atropine dosing in this situation does not have an upper limit. The primary endpoints of atropine therapy are to eliminate respiratory secretions and maintain cardiovascular function (i.e., maintain blood pressure and heart rate) (see Table 18.3) [15, 19, 20].

As evidenced by the Tokyo subway sarin attack in 1995, availability of atropine may become an issue in some facilities given the high doses that might be required and the number of patients that need treatment [2]. In the event that more atropine cannot be obtained, other anticholinergics can be substituted. Glycopyrrolate is one of the alternatives that has been considered and was studied in one small, randomized controlled trial versus atropine, showing no difference in efficacy. Some providers do advocate use of glycopyrrolate in conjunction with atropine to help minimize CNS effects of atropine. From the information we have so far, which is limited, it seems that glycopyrrolate is a reasonable alternative to atropine, especially if atropine supply is limited. Standard dosing for glycopyrrolate in nerve agent or organophosphate pesticide poisoning has not been determined [20].

Another alternative treatment that may be available is scopolamine. It is uncertain if scopolamine would be an effective agent on its own, but some small studies have shown that scopolamine is a useful adjunct to atropine therapy. Scopolamine crosses the blood–brain barrier more readily than atropine and may exert its effect by decreasing CNS symptoms in the acute as well as long-term setting. If atropine is in short supply, it is reasonable to use scopolamine as an adjunct [15, 21].

In the event of severe atropine shortage and large numbers of patients, other alternative treatments may be needed. Most civilian emergency departments have insufficient supply to treat a large number of patients. One study looked at the efficacy of utilizing ophthalmic antimuscarinic agents to treat organophosphate poisoning in rats [22]. In this protocol, four groups of rats were pretreated with saline, atropine, ophthalmic tropicamide, or ophthalmic cyclopentolate solutions. Survival in each of the atropine, tropicamide, and cyclopentolate groups was 90 %, compared to only 10 % in the control group. These preliminary data indicate that parenteral use of ophthalmic solutions may be considered as an alternative to atropine in situations of severe shortages of standard atropine [22].

The other standard therapy for nerve agent or organophosphate exposure is pralidoxime, or other oximes. Oximes act to reactivate acetylcholinesterase by dissociating it from the nerve agent [15]. Reactivation is limited by the aging process of the bond between AChE and nerve agent. Once the bond between nerve agent and acetylcholinesterase is irreversible (i.e., "has aged"), the pralidoxime is no longer effective [15, 20]. Pralidoxime has little to no CNS effect, exerting most of its effects by restoring skeletal muscle function.

In recent years, significant controversy has arisen over the efficacy and safety of oxime use in organophosphate poisoning. Multiple new agents

Table 18.3 Nerve agent antidotes

Nerve agent antidotes	Mechanism of action	Dosing	Side effects
Atropine	Acts at muscarinic receptors by competing with nerve agent	2–8 mg initial dosing IM or IV, re-dosing every 3–8 min until symptoms resolve	Tachycardia, hypertension, high fever, dry mucous membranes, delerium
Pralidoxime	Reactivates acetylcholinesterase	30 mg/kg bolus IV or IM followed by 8 mg/kg/h infusion	Rapid rise in blood pressure (potentially severe), tachycardia, weakness, dizziness, blurred vision

Sources: (1) Munro N, Watson A, Ambrose K, Griffin G. Treating exposure to chemical warfare agents: implications for health care providers and community emergency planning. Environ Health Perspect. 1990;89:205–15. (2) King A, Aaron C. Organophosphate and carbamate poisoning. Emerg Med Clin N Am. 2015;33:133–51. (3) Blain PG. Organophosphorous poisoning. Clin Evid. 2011;05:2102

have been developed showing varying efficacy and varying safety profiles. Patients respond differently depending on the agent of exposure. Overall, the evidence is mixed. There is no evidence good enough to eliminate pralidoxime from the treatment regimen and, as yet, no evidence sufficient to routinely recommend one of the newer oximes over the more traditionally used oximes. Studies are needed to further investigate whether any newer oximes are more broadly active across a spectrum of organophosphates and to further evaluate safety of all of these agents in human subjects. Studies in animals have already begun to focus on both questions [20, 23, 24].

Typical dosing of pralidoxime, according to the World Health Organization (WHO), is 30 mg/kg bolus followed by an 8 mg/kg/h infusion [20]. One small study attempted to evaluate intermittent bolus dosing of pralidoxime, but was not sufficiently powered to recommend this dose over the standard recommended dosing [25]. The WHO also recommends obidoxime as an alternative to pralidoxime. The WHO-recommended dose of obidoxime is a 250 mg bolus followed by 750 mg/24 h. In either case, oxime should be continued until at least 12 h after atropine is no longer required. Continued oxime therapy is warranted for a prolonged period following exposure, even up to 120 h, given that there may be continued reinhibition of AChE at higher concentrations of nerve agent (see Table 18.3) [20, 25].

Nerve agents are among some of the most lethal of the chemical warfare agents. Health care workers should protect themselves fully prior to approaching patients. Primary treatment at present is comprised of immediate decontamination, atropine, an oxime (likely pralidoxime), and supportive care.

18.4 Conclusion

Most health care personnel will never encounter a chemical attack, nevertheless, it is important to be prepared. We must understand the importance of personal protection prior to treatment. If health care workers become patients, our ability to effectively care for patients is only further compromised. Early and close communication between pre-hospital and hospital personnel, when possible, allows early treatment and preparation. Anticipating symptoms and needed treatment, as well as the need for protective gear, is a major step to managing such an event.

Editor's Note: LCDR Jami Hickey, MD is currently serving on Active Duty in the United States Navy. She has served in one combat deployment.

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