Emergency Management of Chemical Weapons Injuries

Peter D. Anderson

Journal of Pharmacy Practice 2012 25: 61 originally published online 11 November 2011
DOI: 10.1177/0897190011420677

Journal of Pharmacy Practice
25(1) 61-68

DOI: 10.1177/0897190011420677
http://jpp.sagepub.com
SAGE

Emergency Management of Chemical Weapons Injuries

Peter D. Anderson, PharmD[1]

Abstract

The potential for chemical weapons to be used in terrorism is a real possibility. Classes of chemical weapons include nerve agents, vesicants (blister agents), choking agents, incapacitating agents, riot control agents, blood agents, and toxic industrial chemicals. The nerve agents work by blocking the actions of acetylcholinesterase leading to a cholinergic syndrome. Nerve agents include sarin, tabun, VX, cyclosarin, and soman. The vesicants include sulfur mustard and lewisite. The vesicants produce blisters and also damage the upper airways. Choking agents include phosgene and chlorine gas. Choking agents cause pulmonary edema. Incapacitating agents include fentanyl and its derivatives and adamsite. Riot control agents include Mace and pepper spray. Blood agents include cyanide. The mechanism of toxicity for cyanide is blocking oxidative phosphorylation. Toxic industrial chemicals include agents such as formaldehyde, hydrofluoric acid, and ammonia.

Keywords

chemical weapons, toxicology, emergency preparedness, CBRNE, homeland security

Continuing Education Learning Objectives

By the end of the article, the reader should be able to:

1. Name several classes of chemical weapons.
2. Describe the clinical presentation, mechanism of toxicity, and treatment of nerve agent poisoning.
3. List the signs and symptoms of vesicant exposure.
4. Discuss the clinical management of cyanide poisoning.
5. Name 4 examples of toxic industrial chemicals.

The United States has been on heightened alert for terrorism since the attacks on September 11, 2001. The anthrax letters that soon followed added to the concerns with terrorism. Terrorism is defined by the Federal Bureau of Investigation as "the unlawful use of force and violence against persons or property to intimidate or coerce a government, the civilian population, or any segment thereof, in furtherance of political or social objectives."[1]

Amid these concerns are preparations by various government agencies and the private section regarding potential attacks with chemical, biological, radiological, nuclear, and high-yield explosives (CBRNE).[2] Management of CBRNE events includes public safety, political, forensic, clinical, disaster response, and environmental issues to name a few. Chemical weapons can include organophosphates (nerve agents), blister agents (eg, nitrogen mustard), choking agents (eg, chlorine), blood agents (eg, cyanide), and toxic industrial chemicals.

Pharmacists are a valuable response when dealing with an actual or potential chemical weapons attack.[3] Their knowledge of chemistry, microbiology, pharmacology, toxicology, and therapeutics makes them an asset to health care facilities and government agencies. This article will focus on the clinical effects of some potential chemical weapons and their treatment.

The aim of this article is primarily to provide an overview of potential chemicals used as weapons. However, much of the knowledge can be applied to situations other than terrorism. Exposure to organophosphate pesticides can occur in industrial or vehicular accidents. Organophosphate poisoning can also result from household accidents or suicide attempts. Exposure to chloride gas can happen in the household by mixing ammonia with bleach. Cyanide poisoning can result as a complication of nitroprusside therapy.

[1] Adjunct Associate Professor of Pharmacy Practice, Pharmacotherapy Consultant/Forensic Pharmacologist, Quincy, MA 02169, USA

Corresponding Author:
Peter D. Anderson, Pharmacotherapy Consultant/Forensic Pharmacologist, 816 Willard Street #207, Quincy, MA 02169, USA
Email: pander7291@aol.com

History of Chemical Weapons

The use of chemical weapons is not new.[4] Crude chemical weapons have been in use for thousands of years. Solon of Athens is believed to have used hellebore roots (a purgative) to contaminate the water supply in the Pleistrus river during the Siege of Cirrha in 590 BC.[5] Modern chemical warfare started during World War I. On April 22, 1915, German soldiers released 150 tons of chlorine gas near Ypres, Belgium. Other chemical weapons used in World War I include phosgene and nitrogen mustard. Between World War I and World War II, new chemical weapons and protective capacities were developed. During World War II, choking agents, vesicants, blood agents, and nerve gas were produced in large quantities. However, no major chemical weapon events occurred during World War II.

In 1993, the Chemical Weapons Convention was finalized.[6] This convention prohibited development, production, stockpiling, and use of chemical weapons. The treaty also mandated the destruction of weapons. In all, 130 countries signed the convention. Neither Iraq nor North Korea signed the treaty.

During the Iraq/Iran war, Iraq used sulfur mustard and nerve agents (taban) against Iran. Aum Shinrikyo, a religious cult dispersed sarin in a residential area in Matsumoto, Japan in 1994. The following year in 1995, sarin was used by terrorists in the subway system in Tokyo, Japan.[4,7]

On October 23, 2002, over 40 Chechen separatists took more than 800 theatergoers hostage in Moscow, Russia.[8] Four days later, special forces of the Russian Federal Security Service (FSB) pumped a derivative of fentanyl into the building. The FSB then stormed by force. A total of 41 terrorists and 129 hostages were killed. All but 2 of the hostages died from opiate toxicity.[9]

The US army defines chemical warfare agents "as toxic substances developed for military use to produce death, serious injury, or incapacitation through their toxicological effects in exposed humans or animals."[10] The limitation of that definition is that many industrial chemicals can in theory be used by terrorists. CBRNE experts commonly have the following classes of chemical weapons: nerve agents, blister agents/vesicants, chocking agents, blood agents, incapacitating agents (eg, Mace), and toxic industrial chemicals. Toxins from a pharmacological or toxicological point can be considered to be chemical weapons. However, most CBRNE experts and the US Army classify toxins such as ricin, botulism toxin, staphylococcal enterotoxin B, mycotoxins, and so on as biological weapons.[11]

Chemical weapons can be classified as persistent or nonpersistent agents.[10] The nonpersistent agents vaporize in the air after a few hours. Persistent agents can remain in the environment for weeks, months, or even years. The persistence of an agent is related to its volatility. The more volatile a given chemical is, the less persistent it is. The less volatile a chemical agent is, the more persistent it is. Most chemical weapons that were originally developed for military use are persistent agents. The reason being is that from a military perspective, the goal was to prevent the progress of enemy forces. Having a chemical weapon that remains in the environment most effectively interferes with the advancing military forces.

Table 1. The comparative volatility of the nerve agents. Sarin is clearly the most volatile. VX is the least volatile nerve agent. VX is much less volatile than the G agents. Comparative LD_{50} of the nerve agents. VX is clearly the most toxic of the nerve agents.

Agent	Volatility (mg/mm ^{3} at 77°F or 25°C)[a]
Tabun (GA)	440
Sarin (GB)	22 000
Soman (GD)	3900
Cyclosarin (GF)	581
VX	10.5
Agents	LD_{50} on Skin, mg[b]
Tabun	1000
Sarin	1700
Soman	50
Cyclosarin	30
VX	10

[a] Data adapted from http://www.atsdr.cdc.gov/mmg/mmg.asp?id=523&tid=93. Accessed August 24, 2011.
[b] Data adapted from US Army Medical Research Institute of Chemical Defense.[10,12,22,31,33,36,41]

Nerve Agents

Nerve agents are organophosphates.[12] They interfere with the acetylcholinesterase (AChE). To understand how nerve agents work, I will review the functions of the cholinergic nerves in the body. Acetylcholine has numerous functions in the body including the primary neurotransmitter of the parasympathetic nervous system. Effects from acetylcholine include muscarinic and nicotinic.[13] Muscarinic is involved with routine body functions such as urination, sweating, digestion, defecation, and causing constriction of the pupil.[14] Muscarinic effects include conservation of resources in the body such as slowing the heart and constriction of the airways. Nicotonic effects include muscle contraction and stimulation of the adrenal gland as part of the flight or fight response. This includes an increase in blood pressure and an increased heart rate. To prevent excessive cholinergic activity, the body destroys acetylcholine with AChE producing choline and acetic acid.[13]

Nerve agents are classified into 2 main categories: the G agents and the V agents.[12] The G agents are nonpersistant agents and the V agents are persistent agents. Many commercially available insecticides are also organophosphates. However, they are much less potent than nerve agents developed as weapons. The G agents include sarin, cyclosarin, soman, and tabun (Table 1). The V agents include VX and VR. Nerve agents can be absorbed orally, by inhalation, or through the skin. The G agents are clear and colorless, whereas VX has a faint amber color. The colors may appear different if the agents are not pure.

The nerve agents prevent the breakdown of acetylcholine resulting in a cholinergic crisis.[12] Muscarinic effects from nerve agents include miosis, bradycardia, diarrhea, nausea and vomiting, diaphoresis, bronchial secretions, and bronchial constriction. A dimming of vision occurs with the miosis.[14] Nicotinic effects include tachycardia and muscle twitching which progresses to muscle paralysis. The toxidrome depends

of the route of absorption. When dermally absorbed muscle twitching occurs first. With inhalation exposure, breathing difficulties are seen first. The onset of symptoms with inhalation exposure is within 5 minutes. With dermal exposure, it can last up to several hours. The seizures due to nerve agents may be from blocking γ-aminobutyric acid (GABA).[15]

Cholinergic agents have a negative chronotropic effect on the heart, that is, slowing of the pulse rate. One may think bradycardia is common with the exposure to nerve agents because of the excessive acetylcholine. However, usually tachycardia occurs with nerve agent exposure. There are several reasons for this. The nicotinic effects result in the release of epinephrine which can cause tachycardia. In addition, the heart rate increases in response to hypoxia and psychological stress. During the sarin attack in 1995, 640 patients were sent to Saint Luke's Hospital in Tokyo. Only 4 patients had bradycardia.[7] Death from nerve agent exposure is usually due to respiratory failure although it can also occur due to status epilepticus. Diarrhea usually is not observed due to nerve agent exposure. The reason being that the person either dies or responds to the antidote before the diarrhea occurs. Six of the patients sent to Saint Luke's Hospital had diarrhea.[7]

The treatment of symptoms due to nerve agent exposure includes atropine to block the muscarinic effects. Atropine, 2mg, is administered every 5 to 10 minutes until respiration improves. Often a cumulative dose 10 to 20 mg of atropine over 2 to 3 hours is needed for clinical response. There is no maximum cumulative dose of atropine for nerve agent exposures. Respiratory function needs to be monitored continuously. Dilation of the pupils must not be used as a guide for continuing atropine. The pupils are slow to respond to intravenous atropine and typically respond only to ophthalmic tropicamide, atropine, or another topical anticholinergic.

Nonpharmacological management includes removal of contaminated clothing.[16] The victims should be washed down with water at the scene. Victims of exclusive vapor exposure do not need to be decontaminated with water but the clothing still should be removed. Rescuers and treatment providers are at risk of exposure, so protection is needed. Airway management such as intubation, oxygen administration, and pulse oximetry is also needed.[16] Suctioning is also needed because of the large amounts of secretions.[15] Intubation and/or ventilation may be difficult until ample amounts of atropine have been administered.[12]

Nicotinic symptoms will not respond to atropine. Pralidoxime (Protopram®) is administered to treat the nicotinic effects.[12] Pralidoxime is often abbreviated as 2-PAM. The dose of pralidoxime is 1 or 2 g over 20 to 30 minutes by intravenous infusion. Rapid administration can result in hypertension and should be repeated in 1 hour if muscle weakness occurs. If intravenous administration is not possible, then pralidoxime can be administered intramuscularly. Pralidoxime belongs to a class of medications called oximes. Other oximes have been studied for treating organophosphates but are not approved by the Food and Drug Administration (FDA). The organophosphates covalently bond with the AChE molecule. This bond becomes permanent after a while. The pralidoxime can reverse the covalent bond before it becomes permanent.

Sarin ages in about 5 hours. Soman ages in about 2 minutes. VX ages in about 40 hours.[17] In many situations with soman exposure it would be impossible to administer within 2 minutes. Therefore, a prophylactic agent for potential soman exposure was developed. Pyridostigmine (Mestinon®) has been originally used to treat muscle weakness from myasthenia gravis. This was granted approval by the FDA as a pretreatment for nerve agent exposure in 2003.[18] Military commanders may order troops to take it without consent if there is a risk of soman exposure. The rationale being that pyridostigmine increases survival with soman exposure. Pyridostigmine is a reversible inhibitor of AChE, whereas nerve agents are an irreversible inhibitor. Having pyridostigmine onboard (taken prior to soman exposure) increases the effectiveness of 2-pralidoxime. Pyridostigmine does not itself treat soman exposure. It will not work if taken after the soman exposure. Pyridostigmine was first used in the Gulf War with a special FDA waiver as an investigational drug. The dose is 30 mg orally every 8 hours. It should be started at least several hours before exposure to the soman.[12]

Pyridostigmine was approved under the "animal efficacy rule."[18] This rule allows animals to be used when studies cannot be conducted on humans because of ethical or feasibility considerations.

The US military issues Mark I kits to certain troops. These kits include autoinjectors for intramuscular atropine and pralidoxime. Certain emergency medical services agencies also use similar Mark I kits.[12]

Seizures are treated with benzodiazepines such as diazepam or lorazepam.[15] For refractory seizures, midazolam or barbiturates can be tried. Phenytoin (Dilantin®) is not to be used for nerve agent poisonings. Most antiepileptic drugs work by increasing the seizure threshold. However, phenytoin works by preventing a seizure focus from spreading.[19] In toxicant-induced seizures, the seizures are global rather than a specific focus. Therefore, phenytoin is not recommended for toxicant-induced seizures.[20]

Ocular pain can be treated with tropicamide 0.5% ophthalmic solution. Atropine or homatropine eyedrops can also be used. However, both atropine and homatropine can aggravate visual impairment.[21]

Blister Agents

The vesicants or blister agents are so called because they produce blisters.[22] Vesicants include nitrogen mustard, sulfur mustard, lewisite, and phosgene oxime. They react with skin, the eyes, and the airways.

Sulfur mustard is also known as mustard gas. Nitrogen mustard is used as a chemotherapy agent, that is, mechlorethamine hydrochloride Mustargen®. However, nitrogen mustard still can be weaponized. The toxic mechanism of action is by binding with the DNA in the cell, preventing cell reproduction. Clinical signs and symptoms of exposure include erythema,

dermal burns, blisters, corneal damage, vomiting, and bone marrow suppression. One key point that needs to be emphasized is that symptoms do not occur immediately. The dermal symptoms may not occur for 8 hours after exposure. Respiratory problems can occur but mustard usually does not get into the lungs, only the upper airways. Sulfur mustard is a bifunctional alklyating agent and cross-links with DNA strands. It can also bind with RNA interfering with cellular repair.[23]

Sulfur mustard is a thick liquid at room temperature but freezes at 58°F. The odor of sulfur mustard can be like garlic, onions, or mustard (hence the name). However, sulfur mustard may not have any odor. Sulfur mustard is often referred to as mustard gas but is not likely to change into a gas at ordinary temperatures.[23] Sulfur mustard is heavier than air and will concentrate in low lying areas. Sulfur mustard is never found naturally in the environment. Sulfur mustard breaks down in water to form hydrochloric acid and thiodiglycol. Sulfur mustard can readily pass through ordinary clothing.

Sulfur mustard can also damage the bone marrow. The white blood cells are affected earlier than the red blood cells. The white blood cells can increase acutely after a sulfur mustard exposure.

Treatment involves washing down the patient and removing contaminated clothing. More severe burns require a surgical consult. Topical antibiotics and steroids may be needed for ocular exposures. Colony-stimulating factors may be needed for bone marrow suppression. Sulfur mustard is rapidly metabolized by the body. The fluid from the blisters does not contain mustard.[22]

Long-term effects of mustard exposure can include relapsing keratitis and heightened sensitivity to pulmonary irritants. Kehe et al[24] describe 12 cases of Iranian patients exposed to sulfur mustard in 1984 or 1985. The first symptom that appeared was on the eyes. Other common manifestations included damage to the bronchial tract and skin. The specific ocular symptoms included lacrimation and burning. The dermal signs included blisters, ulcers, and edema. One patient had hyperpigmentation. All patients had hoarseness and a sore throat. Half the patients had hypoxia. One patient died from septicemia secondary to bone marrow suppression.

No mustard attacks occurred in the United States. However, in 1996, several workers were exposed to mustard gas in industrial accident at the Georgia Gulf facility in Palquemine, Louisiana.[25] Sulfur impurities contaminated the plastic manufacturing process, producing mustard gas. The plant manufactured vinyl chloride monomer, a chemical used for making plastics. Sulfur contamination resulted in the production of mustard gas. Several hundred workers and their families were exposed to sulfur mustard gas.

Rapid decontamination and removal of clothing is a must.[22,23,26] No specific antidotes exist for sulfur mustard gas. Small blisters can be left intact but larger blisters may need to be unroofed. Erythema can be treated with calamine or another soothing lotion or cream. Modified Dakins solution was used in World War I and during the Iraq–Iran War as an irrigation and antiseptic. Fluid and electrolytes need to be monitored. Fluid loss can occur with exposure to sulfur mustard gas. However, the fluid loss is less experienced in patients with thermal burns. Clinicians need to be careful not to overhydrate patients with sulfur mustard injuries.[22]

Treatment of ocular injuries include homatropine (or another topical anticholinergic) and topical antibiotic drops to prevent infection.[22] Petrolatum should be applied to the edges of the lids to prevent them from sticking together. Topical steroids should be limited to 2 days unless further use is recommended by an ophthalmologist. Avoid using topical anesthetics on the eyes unless needed for an ocular examination.

Respiratory support includes intubation, oxygen, continuous positive airway pressure (CPAP), or positive end-expiratory pressure (PEEP). Bronchodilators may be needed if bronchoconstriction occurs. Antibiotics are to be avoided for prophylaxis. Antibiotics can be used if there is clinical evidence of a respiratory tract infection.[22]

If bone marrow suppression occurs consider bone marrow transplants, blood transfusions, or colony-stimulating factors. Sterilization of the gut should be considered if bone marrow suppression occurs.

Hemodialysis was used in some of the Munich patients but the *Medical Management of Chemical Casualties Handbook* specifically advises against using hemodialysis as it can be harmful. Activated charcoal has not been shown to be of value. Nausea and vomiting can be treated with antiemetics.

The chronic effects of sulfur mustard gas are less documented,[27] but data do exist from the exposures during World War I and the Iraq–Iran War. The main long-term effects include ocular, dermal, and respiratory. Neuropsychiatric and immune system reactions can occur. The most common long-term dermal effect is dry skin. Patients may be susceptible to chronic eczema and seborrheic dermatitis. Severe ocular symptoms are reported in less than 1% of patients. The cornea is primarily involved in those cases. Pulmonary manifestations include chronic cough and sputum production. A more serious long-term effect that can occur is bronchiolitis obliterans. This condition is a nonreversible lung disease in which the bronchioles are compressed and narrowed by scar tissues. A study by Mohammadhoseiniakbari et al found decreased lymphocytes (42.8 in controls and 35.9 patients) 25 years after exposure to sulfur mustard gas.[28] Decreased CD4+ counts were also found in the same study. CD4+ is involved in regulating other leucocytes involved in immunity. Sulfur mustard may also be carcinogenic, thus has a risk of causing lung and skin cancers.[23]

Lewisite was first synthesized by Wilford Lee Lewis in the United States in 1918 but too late for use during World War I.[22] Lewisite is a vesicant that contains arsenic.[29] Lewisite is a persistent chemical that poses contact, inhalation, and ingestion hazards. Lewisite is an oily and colorless substance with the odor of germaniums.[29] There are no industrial or commercial uses for lewisite. It is more volatile than sulfur mustard. Similar to mustard agents, lewisite causes damage to dermal, ocular, and airway tissue. However, the onset of symptoms with lewisite is immediate with contact of the eyes or skin. Mustard

agents produce delayed effects. Since the victim experiences pain immediately, they are likely to seek protection and treatment immediately. Lewisite also causes capillary leakage that can result in shock.[30] The antidote for lewisite is dimercaprol, also known as British anti-Lewisite (BAL). Otherwise treatment is similar to mustard agents.

Phosgene oxime is often classified as vesicant, but it does not cause blisters.[22] Phosgene oxime is a nettle agent. A nettle agent causes a corrosive skin or tissue lesion. Phosgene oxime should not be confused with plain phosgene. Phosgene oxime, like phosgene, can cause pulmonary edema. The former is much more irritating to the skin than the latter. No specific antidotes exist for phosgene oxime. The affected skin should be treated the same way a necrotic skin lesion would be treated. Phosgene will be discussed in the next section.

Choking Agents

The asphyxiating or choking agents are so named because they irritate pulmonary tissue and cause the lungs to fill with fluid.[30] The resulting pulmonary edema can result in death by suffocation. The choking agents include chlorine gas, phosgene, and phosgene derivatives. Mustard and lewisite are not classified as a choking agent even though they cause respiratory distress. Mustard and lewisite affect the upper airways rather than the lungs.

Phosgene is a gas that is used industrially in the production of plastics and pesticides. At low concentrations, phosgene has the smell of freshly mown hay or green corn.[31] However, the odor may not be noticed by all individuals exposed. The odor is unpleasant. The main toxic effect from phosgene is pulmonary edema. Phosgene has weak irritating effects on the eyes and mucous membranes. Immediately after exposure, respiratory irritation, headache, and topical irritation occur. However, within 4 to 5 hours of exposure, lesions develop in the alveoli. This pulmonary damage causes symptoms of respiratory distress, tachycardia, and cyanosis. The casualty may notice some airway, nose, or eye irritation at exposure or shortly thereafter. The onset of serious signs and symptoms may not occur for several hours or more (up to 72 hours).[22] In other words, a latent or asymptomatic period occurs after the acute exposure but before the clinical manifestation of the pulmonary edema. Signs of hypovolemia can also occur. Treatment includes mechanical ventilation, fluid replacements, and diuretics. The use of prophylactic corticosteroids is controversial.

Chlorine was the first chemical agent to be used in World War I.[22] Chlorine produces a bleach-like odor and is a green-yellow gas.[32] Chlorine works on both the upper airways and the lower airways. Hydrochloric acid is produced when chlorine reacts with moisture in the airways, which leads to wheezing and coughing. It can also cause pulmonary edema. Treatment is similar to phosgene exposure.

Blood Agents

The blood agents work after being absorbed in the body and transported by the blood.[33] The prototypical agent is cyanide. Cyanide interferes with cellular respiration. Much of the CBRNE literature classifies cyanide as a blood agent. However, this does not make sense from a pharmacological or toxicological point of view. Cyanide does not exert its toxic effects in the blood. In target tissues, cyanide binds with the ferric ion of cytochrome oxidase, impairing oxidative phosphorylation.

Cyanide is used in gold and silver ore extraction, electroplating, fumigation, stainless steel manufacturing, and plant sources (eg, apricot seeds, cassava roots, pits of cherries, and peaches). Combustion from a number of products such as plastics and wool can also produce cyanide. This contributes to the lethalness of smoke inhalation.

Signs and symptoms of cyanide exposure include tachycardia followed by bradycardia, hypotension, cyanosis, metabolic acidosis, and seizures. The cyanide kit contains amyl nitrite, sodium nitrite, and sodium thiosulfate. A vial of amyl nitrite is broken and the vapor inhaled for 15 to 30 seconds. It is repeated every minute until sodium nitrite can be given intravenously. The dose for sodium nitrite is 300 mg. Following administration of the sodium nitrite, the sodium thiosulfate is administered at 12.5 g over 10 minutes. The amyl nitrite and sodium nitrite causes methemoglobulin which "pulls" the cyanide out of the tissues and into the blood. Sodium thiosulfate serves as a sulfur donor for the enzyme rhodanese. Rhodanese is an enzyme naturally found in the body that metabolizes cyanide.

An alternative to the cyanide kit is hydroxocobalamin (Cyanokit) which is FDA approved.[34] Hydroxocobalamin binds with cyanide to form cyanocobalamin which is vitamin B12. The cyanocobalamin is excreted renally. The adult dose for hydroxocobalamin is 5 g (two 2.5-g vials) administered by intravenous infusion over 15 minutes. Depending on the clinical response, a second dose of 5 mg may be administered. A common side effect is transient hypertension. Allergic reactions can also occur including anaphylaxis, chest tightness, urticaria, rash, and edema.

Aggressive oxygenation and airway management is critical. Acidosis caused by cyanide is treated with sodium bicarbonate. Seizures can be treated with diazepam or another injectable benzodiazepine. Hypotension is treated with vasopressors such as norepinephrine.

Cyanides are not the only blood agents. Arsine is also a blood agent.[30] Arsine is formed when arsenic comes in contact with an acid. Arsine was studied as a chemical weapon during World War II, but it was never used as a chemical weapon. Common industrial uses of arsine include semiconductor production and metal refining. When arsine enters the blood, it damages the erythrocytes. Signs and symptoms of exposure include weakness, fatigue, headache, rapid breathing, nausea/vomiting, muscle cramps, red or dark urine, jaundice, renal failure, and muscle cramps.[35] More serious exposures include convulsions, paralysis, unconsciousness, and respiratory failure. A gas similar to arsine is stibine. Stibine is formed when the metal antimony is exposed to an acid. No specific antidote for arsine exists. Supportive care includes blood transfusions and renal dialysis.[35]

Incapacitating Agents

Incapacitating agents are temporary or nonlethal.[36] The goal with incapacitating agents is to impair or cause a disability.[37] Any of the agents discussed in this article obviously cause impairment. However, in a military definition these agents produce a temporary and nonlethal impairment. Riot control agents discussed in the next section have not been considered as incapacitating agents because their duration of action is too short. Although incapacitating agents are considered "nonlethal," perhaps a better way to think of them is less lethal. I will give the following analogy to illustrate this point. The Taser® is considered as nonlethal weapon compared to a bullet from a gun. However, in a susceptible individual (eg, cardiac problems), it can still be lethal. Incapacitating agents that are used for law enforcement are except from the chemical weapons treaty.[38] Incapacitating agents still could be used by terrorists despite their relatively low toxicity. The goals of terrorists are often to induce fear.

Potential incapacitating agents including anticholinergics, fentanyl derivatives, lysergic acid diethylamide, benzodiazepines, and α_2 agonists have also been studied.[38] Incapacitating agents that work as sedatives have also been referred to as "calmatives."[9]

The prototype anticholinergic for military or terrorism use is 3-quinuclidinyl benzilate, which is referred to as BZ from its North Atlantic Treaty Organization (NATO) code. In the scientific community, it is referred to as QNB. The toxic effects of anticholinergics include mydriasis, urinary retention, dry mouth, tachycardia, hallucinations, and impaired memory. Other anticholinergics could in theory be used as chemical weapons. The main consideration whether a given anticholinergic agent can be weaponized is its ability to be dispersed in the air.

Fentanyl derivatives can also be used as incapacitating agents. More than a dozen derivatives of fentanyl have been developed. The Russians used a fentanyl derivative to incapcitate 50 Chechen terrorists[8] during the hostage situation in 2002. Of 800 hostages, 127 died due to exposure to the gas. Signs and symptoms include dizziness, bradycardia, drowsiness, miosis (although mydriasis can occur if hypoxia is present), vomiting, and respiratory suppression. Due to the potential lethality of fentanyl derivatives, it can be argued whether they should be classified as incapacitating agents. The most likely fentanyl derivative to be weaponized is carfentanil.[9] Although the fentanyl derivative could have been sufentanil, alfentanil, or remifentanil.[9] Treatment of toxicity includes naloxone and respiratory support.

The number of fatalities is high despite being considered a nonlethal agent. Several factors may have contributed to the degree of mortality. The air currents may have created areas of high concentrations of carfentanil. The hostages had limited food and water for 3 days. The hostages were mostly immobile for 3 days. The Russian government did not immediately disclose the use of a fentanyl derivative.[39] Some of the clinicians treating the victims thought that a nerve agent was used.[9] Opiates cause miosis as does nerve agents. Atropine was actually given to some of the patients. Both opiates and nerve agents can cause respiratory problems. With opiates, such as fentanyl, the effect is mainly through suppression in the medullas. As discussed above, the respiratory distress from nerve agents is related to airway constriction, bronchial secretions, and paralysis of the diaphragm. Halothane may have been used in addition to the fentanyl derivative.[9,40] Both nerve agents and opiates can cause bradycardia. However, nerve agents are more likely to cause tachycardia.

Riot Control Agents

Riot control agents are designed to cause transient discomfort and eye closure, rendering the subject unable to resist arrest or prevent fighting.[41] Law enforcement officers used riot control to subdue suspects resisting arrest to mitigate riots. Military forces use riot control agents for training and in combat. Riot control agents are also referred to irritants, lacrimators, or "tear gas." They also cause irritation to the skin, lungs, throat, and mouth.

Perhaps the most well-known riot control agent is chloracetophenome (CN) which is commonly referred to by its brand name Mace®. Other riot control agents include chlorobenylidene maloritrile (C5), chloropicrin (also used as a fumigant), bromobenzylcyanide (CA), oleoresin capsaicin, diphenylaminearsine, and dibenzoxazepine.[41,42] The effects of riot control agents typically last 15 to 45 minutes after the person is removed from the contaminated environment and cleaned off.

Exposure to riot control agents causes lacrimation, burning (eyes, nasal passages, mouth, skin), blurred vision, bloodshot eyes, drooling, rash, and nausea/vomiting. Treatment includes rinsing the eyes with water for 15 minutes, removal of contacts if worn, removal of affected clothing, and washing of the skin with soap and water. More severe cases may warrant the treatment with supplemental oxygen or bronchodilators. Burns on the skin would be treated like other burns. [41,42]

Toxic Industrial Chemicals

Toxic industrial chemicals are chemicals that are not traditionally thought of as chemical weapons. They were not developed as chemical weapons.[43] Most have commercial uses. They were not designed as chemical weapons so most of them are not persistent. However, they are easier to obtain than traditional chemical weapons. Toxic industrial chemicals can be very dangerous and are often produced in large quantities. Some toxic industrial chemicals have explosive hazards. Certain toxic industrial chemicals can include specific precursors to other chemical weapons. For example, hydrofluoric acid is needed for the synthesis of sarin. Terrorists may make use of industrial chemicals for either their toxic or their explosive hazards. Other toxic industrial chemicals may be used in the synthesis of more dangerous agents.

Examples of toxic industrial chemicals include fluorine, ammonia, formaldehyde, tungsten hexafluoride, sulfuric acid, and tetramethyl lead.[43] Detailed discussions of these and other agents are outside the scope of this article. However, hydrofluoric acid will be discussed briefly.

Hydrofluoric acid is a weak acid but still quite toxic. Commercial uses of hydrogen fluoride include glass etching, metal cleaning, and manufacturing of electronics. Hydrogen fluoride can readily penetrate the skin. It binds with calcium and magnesium. The primary treatment is calcium gluconate. Hypocalcemia can lead to cardiac arrthymias.[44]

The take-home message is potential, chemical weapons are in no way limited to the traditional agents that we think of as chemical weapons.

Strategic National Stockpile

The Centers for Disease Control and Prevention (CDC) maintains a Strategic National Stockpile.[45] In addition to pharmaceuticals, stockpile includes medical equipment and supplies. The supplies can be sent to any state of the union within 12 hours with the push packages. US Marshals Service provides security for the packages during transport from their storage site to delivery to the affected state. Each state has plans on how to receive and distribute the material to local communities. The formulary of the national stockpile is decided on current threats, the vulnerability of the population, and supply needs. The stockpile includes antibiotics, airway maintenance equipment, intravenous administration sets, surgical supplies, vaccines, antidotes, and radioprotectants. The stockpile can be used in a terrorist attack, influenza outbreak, earthquake, or other disaster. The stockpile is also backed by vendor agreements with the CDC. The CDC works with other government agencies including the Military Vaccine Agency, FDA, and the Department of Homeland Security.[45]

Conclusion

Potential antidotes needed to be stocked in the hospital include atropine, pralidoxime, diazepam, midazolam, cyanide kits, hydroxocobalamin, vasopressors, and sodium bicarbonate.

A wide variety of chemical agents can be used as chemical weapons. Pharmacists can work in their hospitals to prepare emergency plans for their hospitals. Pharmacists can also work with the pharmacy and therapeutic committees to stock for a potential chemical accident or terrorist attack.

Declaration of Conflicting Interests

The author declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

References

1. Federal Bureau of Investigation. Terrorism 2002–2005. http://www.fbi.gov/stats-services/publications/terrorism-2002-2005/terror02_05. Accessed October 8, 2010.
2. US Army 20th Support Command. www.cbrne.army.mil. Accessed November 17, 2010.
3. Burda AM, Sigg T. Pharmacy preparedness for incidents involving nuclear, biological, or chemical weapons. *J Pharm Pract*. 2004;17(4):251-265.
4. Krenzelok EP. *History of Biological and Chemical Terrorism. Biological and Chemical Terrorism: A Pharmacy Preparedness Guide*. Bethesda, MD: American Society of Health System Pharmacists; 2003:3-8.
5. A Brief History of Chemical and Biological Weapons (2001). http://www.cbwinfo.com/History/History.html. Accessed December 17, 2010.
6. Organisation for Prohibition of Chemical Weapons. http://www.opcw.org/chemical-weapons-convention/. Accessed October 12, 2010.
7. Okumura T, Takasa N, Ishimatsu S, et al. Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med*. 1996;28:129-135.
8. Donahoe JJ. The Moscow hostage crisis: an analysis of Chechen terrorist goals. *Strategic Insights*. 2003. 2(5). http://www.nps.edu/Academics/centers/ccc/publications/OnlineJournal/2003/may03/russia.htm. Accessed October 12, 2010.
9. Wax PM, Becker CE, Curry SC. Unexpected "gas" casualties in Moscow: a medical toxicology perspective. *Ann Emerg Med*. 2003;41(5):700-705.
10. US Army Medical Research Institute of Chemical Defense. *Chemical Agents–General Concepts and Terminology. Medical Management of Chemical Casualties Handbook*. 4th ed. MD: U.S. Army Medical Research Institute of Chemical Defense, Chemical Casualty Care Division, Aberdeen Proving Ground; 2007;4-5.
11. US Army Medical Research Institute of Infectious Diseases. *Biological Toxins. USAMRII's Medical Management of Biological Casualties Handbook*. 6th ed. Frederick, MD: U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick. 2005; 166-203.
12. US Army Medical Research Institute of Chemical Defense. *Nerve Agents. Medical Management of Chemical Casualties Handbook*. 4th ed. MD: U.S. Army Medical Research Institute of Chemical Defense, Chemical Casualty Care Division, Aberdeen Proving Ground; 2007; 122-156.
13. Westfall TC, Westfall DP. Neurotransmission—the autonomic and somatic motor nervous systems. In: Brunton LL, Lazo, JS, Parker KL. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 11th ed. New York: McGraw Hill Medical; 2006:137-182.
14. Brown JH, Taylor P. Muscarinic receptor agonists and antagonists. In. Brunton LL, Lazo JF, Parker KL. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 11th ed. New York: McGraw Hill Medical; 2006:183-200.
15. Lee AC. Clinical manifestations of sarin nerve gas exposure. *JAMA*. 2003;290(5):659-662.
16. Tokuda Y, Kituchi M, Takahashi O, et al. Prehospital management of sarin nerve gas terrorism in urban setting: 10 years of progress after the subway sarin attack. *Resuscitation*. 2006;68:193-202.
17. Agency for Toxic Substances and Disease Registry. *Case Studies in Environmental Medicine (CSEM) Cholinesterase Inhibitors Including Insecticides and Chemical Warfare Nerve Agents*. http://www.atsdr.cdc.gov/csem/cholinesterase/pam_medications.html. Accessed January 17, 2011.

18. Food and Drug Administration. FDA Approves Pyridostigmine bromide as pretreatment against nerve gas. http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm130342.htm. Accessed December 10, 2010.
19. Rao RB. Neurologic principles. In: Hoffman RS, Nelson LS, et al, eds. *Goldfrank's Manual of Toxicologic Emergencies*. New York: McGraw Hill Medical; 2007:171-176.
20. Greene S, Kerr F, Koutsogiannis Z, Robinson J. Phenytoin in toxin-induced seizures. *Emerg Med Australas*. 2010; 22(4):354.
21. Huebner KD, Arnold JA. CBRNE-nerve agent, G-series-Tabun, Sarin, Soman. http://emedicine.medscape.com/article/831648-overview. Accessed October 12, 2010.
22. US Army Medical Research Institute of Chemical Defense. *Vesicants. Medical Management of Chemical Casualties Handbook*. 4th ed. 2007;62-121.
23. Rosemond ZA, Beblo DA, Amata R. Toxicological profile for sulfur mustard. Agency for Toxic Substances and Disease Registry. 2003.
24. Kehe K, Thiermann H, Balszuweit F, et al. Acute effects of sulfur mustard injury—Munich experiences. *Toxicology*. 2009;263(1):3-8.
25. Coleman Z. Georgia Gulf Ready to Settle Chemical Suits. Atlanta Business Chronicle. http://bizjournals.com/atlanta/stories/1999/06/07/story7.html date. Accessed November 26, 2010.
26. Centers for Disease Control and Prevention. Sulfur Mustard (Mustard Gas). www.bt.cdc.gov/agent/sulfurmustard. Accessed November 26, 2010.
27. Rowell M, Kehe K, Balszuweit F, et al. The chronic effects of sulfur mustard exposure. *Toxicology*. 2009;263(1):9-11.
28. Mohammadhoseiniakbari H, Ghanei M, Eajazi A, et al. Delayed effects of sulfur mustard poisoning on CD4+ and CD8+ lymphocytes in Iranian veterans 25 years after exposure. *Med Sci Monit*. 2008;14(11):CR580-CR583.
29. Centers for Disease Control and Prevention. Facts about Lewisite. http://www.bt.cdc.gov/agent/lewisite/basics/facts.asp. Accessed January 17, 2011.
30. Mccafferty RR, Lennarson PJ. Common chemical agent threats. *Neurosurg Focus*. 2002;12(3):21.
31. US Army Medical Research Institute of Chemical Defense. *Lung-Damaging Agents. Medical Management of Chemical Casualties Handbook*. 4th ed. 2007; 18-39.
32. Centers for Disease Control and Prevention. Facts about Chlorine. http://www.bt.cdc.gov/agent/chlorine/basics/facts.asp. Accessed January 17, 2011.
33. US Army Medical Research Institute of Chemical Defense. *Cyanide. Medical Management of Chemical Casualties Handbook*. 4th ed. 2007; 40-61.
34. Cyanokit. Meridian Medical Technologies, Columbia, MD.
35. Centers for Disease Control and Prevention. Facts about Arsine. http://www.bt.cdc.gov/agent/arsine/facts.asph. Accessed October 12, 2010.
36. US Army Medical Research Institute of Chemical Defense. *Incapacitating Agents. Medical Management of Chemical Casualties Handbook*. 4th ed. 2007; 157-193.
37. Centers for Disease Control. Facts About Riot Control Agents: Interim Document. http://www.bt.cdc.gov/agent/riotcontrol/factsheet.asp. Accessed October 12, 2010.
38. Dando M. Biologists napping while work militarized. *Nature*. 2009;460(7258):950-951.
39. Gross ML. Non-lethal weapons and the civilian death toll in war time. *Nature*. 2009;461(7262):340.
40. Schiermeir Q. Hostage deaths put gas weapons in spotlight. *Nature*. 2002;420(6911):7.
41. US Army Medical Research Institute of Chemical Defense. *Riot Control Agents. Medical Management of Chemical Casualties Handbook*. 4th ed. 2007;194-211.
42. Centers for Disease Control and Prevention. Riot Control Agents. http://emergency.cdc.gov/agent/riotcontrol/index.asp. Accessed January 16, 2011.
43. Occupational Safety and Health Administration. Toxic Industrial Chemicals. http://www.osha.gov/SLTC/emergencypreparedness/guides/chemical.htm. Accessed October 7, 2010.
44. Wilkes G. Hydrofluoric Acid Burns. http://emedicine.medscape.-com/article/773304-overview. Updated January 28, 2010. Accessed November 26, 2010.
45. Centers for Disease Control and Prevention. Strategic National Stockpile. http://www.bt.cdc.gov/stockpile/. Accessed January 17, 2011.

Continuing Education Credit

The New York State Council of Health-system Pharmacists (NYSCHP) is pleased to provide you with the opportunity to obtain continuing education credit for this article online at HealthSystemCE.org (http://www.healthsystemce.org); login using your email address and HSCE password; then click the ''Journal CE'' tab. There is no charge to NYSCHP members. If you are not a member of NYSCHP, call 1-518-456-8819 to pay the $15 fee to access the quiz and obtain the password necessary to access the Journal's CE article. In lieu of this fee, a completed membership application with your dues may be submitted.

A grade of 70% or above is required to earn the CE credit. Repeat examinations will be permitted once for a grade below 70%.

The NYSCHP is approved by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program provides 1.6 contact hours (0.16CEUs) of continuing education. Universal Program Number is 0134-0000-11-057-H04-P. Submission of exam for CE credit expires 7/31/2014.