Antidotes and Treatments for Chemical Warfare/Terrorism Agents: An Evidence-Based Review

GC Rodgers Jr1 and CT Condurache1

This article reviews the evidence supporting the efficacy of antidotes used or recommended for the potential chemical warfare agents of most concern. Chemical warfare agents considered include cyanide, vesicants, pulmonary irritants such as chlorine and phosgene, and nerve agents. The strength of evidence for most antidotes is weak, highlighting the need for additional research in this area.

The usual definition of a chemical warfare agent is a chemical agent intended for use in military operations that is designed to seriously injure, kill, or incapacitate opposing forces. Many agents originally designed for classic warfare are now also considered potential weapons in terrorist operations. The concept of chemical warfare has existed for several thousand years. Excellent reviews have been published.1,2 The Chinese reportedly used toxic smoke, including arsenic compounds, as early as in 1000 bc. Over the centuries, many others have employed toxic smoke or vapors in limited ways and with inconsistent results. Various toxins have also been used in attempts to poison water or food sources, with the intent of killing or incapacitating the enemy and often the supporting civilian population as well. The eighteenth and nineteenth centuries saw the emergence of chemistry as a branch of science, and during this period chlorine, hydrogen cyanide, phosgene, and, subsequently, the mustard agent chloropicrin and many other compounds were discovered. Several proposals were made to use chemical weapons during the American Civil War, but none were actually used.3

Table 1 summarizes the more modern uses of chemical warfare agents. Since World War I (WWI), a number of international agreements, beginning with the Geneva Protocol in 1925, have attempted to limit the development and use of chemical weapons, with limited success.4 This review focuses on four groups of chemical warfare agents: chemical asphyxiants (cyanide and its various precursors), vesicants (sulfur mustard and Lewisite), pulmonary toxins (chlorine and phosgene), and nerve agents (organophosphates (OPs)). Although other chemical agents have been used or proposed, such as ricin, botulinum toxin, and picric acid, these are generally not considered to have significant potential as warfare or terrorism agents and are not considered here. Biological agents are also not discussed in this review.

OVERVIEW OF EVIDENCE FOR EFFICACY OF ANTIDOTES AGAINST CHEMICAL WARFARE AGENTS

As is common in many aspects of toxicology, there is a dearth of good data on the efficacy of antidotes and treatment options for use against chemical warfare agents.5 The gold standard for evidence-based medicine is the prospective randomized controlled trial (RCT) comparing the effectiveness of a new intervention with those of a standard treatment, a placebo, or no treatment, for a given condition. Both ethics and practicality prohibit the use of prospective randomized trials in humans treated for exposure to chemical warfare agents, although studies have been carried out in relation to some of these chemical agents by military groups in human subjects.6 Fortunately, the opportunities in recent years to conduct such trials on patients poisoned as part of some large-scale terrorist or military action have been rare. As a result, in trying to assess the efficacy of standard or proposed antidotes or treatments, we are left with less-than-perfect data in humans, usually case reports or small case series, or, in some cases, none at all. Because all the chemicals of concern are potentially lethal, one must be cautious in drawing conclusions from individual cases. Also of concern is the fact that much of the existing data in humans relate to scenarios with much missing data, including the timing and quantity of the exposure. This makes the analysis of such data problematic. For instance, the proposed antidotes may appear ineffective if not given within an appropriate time frame. If the timing of the exposure is not known, it is difficult to assess such outcome data. For many antidotes or proposed treatments, there are data from animal experiments that we can use to assist in assessments. A major area of current research interest is prophylactic treatments, particularly for use by military personnel. This article does not consider possible pre-exposure protective agents or treatments.

1Department of Pediatrics, University of Louisville School of Medicine, Louisville, Kentucky, USA. Correspondence: GC Rodgers Jr (gcrodgers@pol.net)

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Cyanide Poisoning

From a toxicology point of view, cyanide is a potent noncompetitive inhibitor of cytochrome c oxidase and a number of other enzymes. Inactivation of cytochrome oxidase leads to tissue hypoxia, tissue dysfunction, and ultimately death. Cyanide is rapidly absorbed from the lung or gastrointestinal tract, and there is a rapid onset of symptoms involving the central nervous system (CNS) and cardiovascular systems, as well as profound metabolic acidosis. Death can occur within a few minutes. Cyanide is metabolized primarily by the enzyme rhodanese in the presence of a sulfur source, forming the relatively nontoxic metabolite thiocyanate.

Cyanide can originate from several sources. It is found in industry in the form of a variety of salts. Cyanide also forms compounds with halogens, such as cyanogen chloride (a gas) and cyanogen bromide (a liquid). Coupled with organic moieties, it forms a variety of nitriles, such as acetonitrile, a common organic solvent and chemical intermediate. The metabolism of some nitriles in humans produces cyanide in vivo. Cyanide is a common component of smoke from burning nitrogen-containing fuels, such as many plastics. In fact, the most common current cause of cyanide poisoning is smoke inhalation.

Cyanide in its various forms is considered a likely agent for terrorist use. It is relatively easy to obtain and handle, and it can be delivered in a variety of forms through different routes. Hydrogen cyanide released into a closed space, such as a building through the HVAC (heating, ventilating, and air-conditioning) system, could result in large-scale casualties. Cyanide has been infrequently used in warfare. The gaseous form, hydrogen cyanide, was tried by the French military during WWI with little effect, because it is lighter than air and rapidly dissipates.

The first commercially available treatment for cyanide poisoning was amyl nitrite, first described as an antidote in 1888 and marketed in combination with sodium nitrite and sodium thiosulfate. The nitrites presumably produce methemoglobin, which binds cyanide, which is then released and metabolized by rhodanese with the help of thiosulfate. This combination was initially marketed as the Lilly Cyanide Antidote Kit (CAK) by Eli Lilly. The amyl nitrite, administered by inhalation, is to be used as the initial treatment, followed by intravenous sodium nitrite and sodium thiosulfate. There are no reported clinical studies of the efficacy of the CAK, although there are several case reports and small case series describing the apparent effectiveness of sodium thiosulfate with or without amyl nitrite or sodium nitrite in cases with measured and potentially lethal cyanide blood levels. Animal studies also support the efficacy of sodium thiosulfate given with sodium nitrite. Sodium thiosulfate given alone in animal studies has had inconsistent results. It has been speculated that this may be because of the slow access of the thiosulfate, which remains primarily in the extracellular spaces, to the rhodanese, which is intracellular.

There has also been no study on the safety of the CAK, although concerns have been raised about the potential for complications from the use of nitrite. It is thought that a level of at least 15% methemoglobin is necessary for the effectiveness of either amyl nitrite or sodium nitrite in cyanide poisoning. Excessive doses of sodium nitrite may produce methemoglobin levels capable of significantly impeding oxygen transport. This is of particular concern in fire/smoke inhalation victims, in whom other risk factors, particularly carbon monoxide exposure, may significantly increase the risk of hypoxia. The risk of hypoxia under these circumstances will depend on the rate of decline of carboxyhemoglobin relative to the rate of increase of methemoglobin, both of which are difficult to predict. Sodium thiosulfate as a stand-alone antidote has been studied and was found to be relatively nontoxic. Although the available data for the efficacy of the CAK are not robust, the findings are generally consistent and strongly suggest that this antidote is effective if used promptly and properly.
In Germany, 4-DMAP is available commercially as an antidote for cyanide poisoning. Like nitrites, 4-DMAP is a methemoglobin generator. 4-DMAP is usually administered intramuscularly, either as a single agent or in combination with thiosulfate or dicobalt edetate. No human studies with this agent have been reported, although there are some case reports and series.16,34,35 There are limited data from animal studies for 4-DMAP; one of the studies reported 100% survival in dogs given a lethal cyanide dose intravenously, followed by the antidote.36 4-DMAP has been reported to have significant toxicity, including unpredictable levels of methemoglobin formation.17 Although the limited data in humans suggest that 4-DMAP can be an effective antidote, its toxicity potential may make it a less desirable alternative.

Dicobalt edetate (Kelocyanor) has been available as a cyanide antidote for several years in Great Britain and France. It is presumed to act by complexing cyanide to form cobalt cyanide, which is then excreted in the urine. It is administered intravenously with glucose to prevent hypoglycemia caused by cobalt toxicity. There have been no studies with dicobalt edetate in humans. Seven case reports provide the only published data in humans.37–42 Of the seven patients, four survived. Dicobalt edetate has been associated with significant toxicities, including cardiac toxicity, seizures, hypoglycemia, and anaphylaxis.17,31 Given that the commercial product contains uncomplexed cobalt, care needs to be taken to not administer the product to patients who may not have been exposed to cyanide poisoning because serious cobalt toxicity may occur.

For more than 30 years, hydroxycobalamin has been known, from animal studies, to be an effective antidote for cyanide poisoning.27,43 Hydroxycobalamin has a higher affinity for cyanide than do tissue cytochromes, thereby competitively binding and inactivating both free and cytochrome-bound cyanide. The cyanocobalamin formed is readily excreted by the kidney. The product became commercially available in 1996 in France and in 2007 in the United States. Because this is a relatively recent antidote, there are more robust data for hydroxycobalamin in humans. The data include those from two uncontrolled studies, both in patients with smoke inhalation and presumed cyanide exposure and in some case reports and small series.44-49

Borron et al. reported on 69 patients with smoke inhalation and presumed cyanide exposure who were treated in an uncontrolled, prospective, open-label study in Paris.48 The patients received 5–15 g of hydroxycobalamin, either before reaching the hospital or in the emergency room. Of 69 patients, 50 (72%) survived, 41 of them with no reported sequelae. Of the patients treated, 37 were comatose at presentation, and 14 had an initial cardiopulmonary arrest. In a retrospective uncontrolled study, also from Paris, Fortin et al. reported on 101 patients with smoke inhalation with presumed cyanide exposure, treated in the prehospital setting with 5 g hydroxycobalamin.45,50 Of the 101 patients, 30 survived, 42 died, and the survival status of the remainder was unknown. Thirty-eight patients were found in cardiac arrest. Only 2 of this group survived. Of the 12 patients who were hemodynamically unstable at the scene, 9 showed a return of adequate blood pressure after administration of hydroxycobalamin. Among the 18 noncomatose patients with some initial neurological impairment, 9 showed improvement in their Glasgow coma scale after the administration of hydroxycobalamin, 8 had no change, and 1 became worse. Minor adverse effects were observed in 6 patients.

Both these studies share some flaws. Neither study measured blood cyanide levels, making it impossible to determine the severity of cyanide toxicity or even the presence of cyanide. Neither study included a control group, and both studies were in patients with smoke inhalation, in whom the presence of many other potentially toxic chemicals, including carbon monoxide, may have significantly affected the outcomes. These flaws aside, both studies provide some suggestion that hydroxycobalamin may be an effective antidote in patients who have not reached the stage of cardiovascular collapse. Both studies suggest that the safety profile for hydroxycobalamin is probably superior to those of the other antidotes discussed. To investigate the potential adverse effects of hydroxycobalamin, Uhl et al. conducted a randomized, double-blind, placebo-controlled, ascending-dose study in 136 healthy volunteers. (The remaining references for this article may be found in the Supplementary References online.) No significant toxicity was observed. As pointed out by several authors, hydroxycobalamin has an advantage over the CAK and 4-DMAP in that it does not further compromise oxygen transport. This makes hydroxycobalamin an ideal agent for prehospital use, an attribute of particular value in the event of a terrorist event.

In summary, the limited data available in humans on all of the currently available antidotes for cyanide indicate that they all have efficacy. Data from animal studies support this conclusion. There are no comparative studies in humans. Toxicity data, and concerns about alteration of oxygen transport, suggest that hydroxycobalamin should be the preferred antidote. Additional studies are needed to compare efficacy in humans and to explore the potential value of combining hydroxycobalamin with thiosulfate.

**VESICANTS**

Vesicants, as a class, cause damage to the skin and mucous membranes resulting in blistering lesions. Although many vesicant agents have been described as potential weapons, only two, sulfur mustard (mustard gas, HD, yperite, yellow cross, dichloroethylsulfide) and Lewisite (2-chlorovinyl dichloroarsine) are discussed in any detail in this article. Of these two, sulfur mustard, which was first synthesized in 1822, has been used more extensively, and its use has been documented in at least 10 conflicts beginning in 1917. Sulfur mustard is an alkylating agent with both cytotoxic and mutagenic properties, and it is a known carcinogen. When used militarily, sulfur mustard produces extensive damage to the skin, eyes, and respiratory tract. The toxicology of sulfur mustard has been reviewed. Extensive exposure can cause systemic effects to other organs and to the bone marrow. Although the pathology of injuries is well known, the mechanisms involved are not clearly defined, despite extensive and ongoing research.
There are currently no recognized antidotes for sulfur mustard. However, on the basis of animal studies and analogy from their use in chemotherapy to protect against the toxic side effects of alkylating agents, thiosulfate and N-acetyl-L-cysteine have been proposed as having possible antidotal effects. Amifostine, an aminothiol, has also been shown to have protective effects against sulfur mustard in rats and mice. Limited animal data suggest that both thiosulfate and N-acetyl-L-cysteine may have some value in treating sulfur mustard exposures, but there are no corroborative human data, and their use is not currently recommended.

Treatment strategies for vesicant exposure are currently directed at minimizing the risks of either acute or chronic sequelae of exposure. The current recommendations are based on anecdotal reports from treatment of exposed populations as well as from animal studies. Much research in the last decade, in various in vivo and in vitro animal models, has been focused on the investigation of protective agents for dermal injury. Historical recommendations have focused on immediate decontamination of the skin. Various authors have recommended simple soap and water, oil or gasoline, diluted household bleach (0.5% sodium hypochlorite), permanganate solutions, iodine preparations, and various adsorbents such as Fuller’s earth, t alc, activated charcoal, and flour for initial decontamination. An animal study comparing the efficacy of skin decontamination with water and with 0.5% sodium hypochlorite (diluted household bleach) in preventing skin injury from sulfur mustard found no difference between the two treatments. A number of absorbent or barrier preparations have also been developed and reportedly tested by military groups for decontamination. Treatment of skin burns from sulfur mustard has generally paralleled treatment of thermal burns.

A number of studies in animal skin models have looked at the efficacy of topical iodine preparations in preventing or minimizing dermal burns from sulfur mustard. Although it was originally thought that iodine chemically inactivates sulfur mustard, it is now clear that this is not so. Although the animal data suggest that iodine preparations would be useful in the early treatment of sulfur mustard burns, there are no data in humans. Another agent traditionally used has been silver sulfadiazine. A comparison study of topical iodine and silver sulfadiazine in a pig skin model found iodine to be superior as an antidote to sulfur mustard, although with limited effect. Early surgical debridement and dermabration have also been recommended, on the basis of data from pig skin models. Sollmann reported experimental evaluation, in human student volunteers, of a wide variety of potential initial treatments for sulfur mustard dermal exposure. Many details of these experiments are not reported; however, the conclusions of the author were that three general methods have some value in preventing injury from dermal sulfur mustard exposure: rapid wash with soap and water, use of oils (such as olive or castor oil), and use of solid adsorbents (such as charcoal, talcum, and zinc oxide). In summary, there are very limited useful data on which to base a firm recommendation about initial treatment options for dermal exposure and injury caused by sulfur mustard. Sodium hypochlorite solutions appear to chemically inactivate sulfur mustard during initial decontamination, and iodine preparations appear to have some value in reducing damage from exposure, but the quality of the data is poor regarding both interventions.

Acute treatment of eye exposures to sulfur mustard has been the subject of considerable concern, but little research. Acute eye injury is the most incapacitating effect of most military sulfur mustard exposures. Sulfur mustard has also been noted to cause many long-term ophthalmologic problems in individuals gassed in military operations or occupationally exposed to the agent. It is generally agreed that sulfur mustard is very rapidly taken up by eye tissues, allowing only a very brief period during which decontamination is of any value in removing the material and preventing injury. A wide variety of flushing solutions have been recommended in the literature on the basis of anecdotal reports, including water, normal saline, 1.5% sodium bicarbonate solution, saturated sodium sulfate or magnesium sulfate solutions (hypertonic solutions), boric acid solutions, 0.5% dichloramine-T solution in a solvent, and dilute solutions of sodium hypochlorite or potassium permanganate.

There are no studies in either animals or humans systematically evaluating the benefits of any of these treatments or comparing them with one another. Recommendations for treatment of the affected eye after decontamination are varied and include steroids, antibiotic ointments, topical analgesics, and even no treatment at all. Studies in a rabbit model have shown the potential benefits of anti-inflammatory drugs such as dexamethasone and diclofenac. These studies showed some biochemical and pathological evidence of effectiveness, but neither drug treatment decreased corneal erosions. Anti-inflammatory drugs have shown good effects in other forms of irritant eye injury. In summary, there are no human data on which to base recommendations for the decontamination of eyes exposed to sulfur mustard. General toxicologic experience would indicate that prompt flushing is likely to have some value and is unlikely to cause additional harm. Animal data with sulfur mustard indicate that the window of opportunity to remove the unabsorbed compound is very short, perhaps ≤5–10 min. In the absence of other information, and considering practical possibilities, it is reasonable to recommend a simple water or saline flush. The quality of the available data is very poor.

The third major exposure route for vesicants, including sulfur mustard, is respiratory. Sulfur mustard causes significant pulmonary pathology if inhaled. There is also a significant risk of long-term pulmonary complications after acute exposure. There is no specific treatment for the respiratory symptoms of sulfur mustard inhalation. Many authors have recommended steroids and antibiotics in addition to general respiratory support. There are no studies in either animals or humans to demonstrate the benefits of these therapies after sulfur mustard inhalation, although data from other types of inhalation injury suggest that they might be useful.

Even more limited information is available for Lewisite because it has seen only limited military use. Lewisite is an organic arsenical compound, first developed as a potential military agent in 1918 by Lee Lewis, with both vesicant toxicity
and significant systemic toxicity. Its only documented military use was by Iraq during its wars with Iran. During the early years of WWII, British researchers successfully developed an antidote to Lewisite, British anti-Lewisite (BAL). BAL (dimercaprol or 2,3-dimercaptopropanol) contains two sulfhydryl groups that form a complex with and inactive arsenic. BAL has subsequently been successfully used to form complexes with other heavy metals, most notably lead. It was extensively tested during WWII, including in humans. These data, reported only in military documents, have been well reviewed, e.g., by Peters. There are abundant published data related to humans documenting the effectiveness of BAL at chelating lead and mercury; however, there are sparse published data regarding its effect on arsenic. In one study, 48 patients with arsenic-induced encephalopathy were treated successfully with BAL. Peters describes testing done during WWII using a BAL ointment, resulted in favorable outcomes with respect to control of skin and eye damage after exposure to arsenic. However, no details of these experiments have been published.

Stocken and Thompson reported experiments in rats with BAL being applied topically 1 h after Lewisite treatment. Although they do not comment on the appearance of the skin, analysis of the skin 48 h later showed that BAL treatment significantly reduced the residual bound arsenic in the skin. Inns et al. compared the efficacy of BAL with that of two newer chelators—meso-2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-propanesulfonic acid (DMPS), both water-soluble analogs of BAL—regarding their ability to prevent systemic toxicity in a rabbit model. Their study employed both intravenous and percutaneous routes of administration of Lewisite. Although all three chelating agents showed comparable protective effects on survival at equivalent doses, the authors were of the opinion that DMSA and DMPS were superior antidotes because of their lower toxicities relative to BAL. The rabbit data also showed that, at higher doses of DMPS and DMSA (doses that are not possible for BAL, given its toxicity), survival was significantly higher.

Aposhian et al. studied the protective effects of BAL, DMSA, and DMPS on the toxicity caused by sodium arsenite in mice; they also concluded that both DMSA and DMPS were superior to BAL, with DMSA being the most effective antidote. Nelson et al. showed, in a guinea pig model, that hypothermia protects against Lewisite-induced skin injury. In that model, protection was further enhanced by the cutaneous application of DMSA. In summary, there are limited data from human and animal studies that BAL is an effective chelating agent for arsenic compounds. It is reasonable to conclude that BAL will be beneficial in preventing or minimizing systemic toxicity from Lewisite. Other than Peters’s secondhand reports, there are no published data on the effect of BAL or any chelator on the dermal and ocular toxicity of Lewisite. There is a reasonable volume of data from animal studies indicating that the less toxic water-soluble analogs of BAL, namely, DMSA and DMPS, are likely to be better antidotes for Lewisite. There are no data reporting specific skin and eye decontamination methods for Lewisite; however, it is likely that any recommendations made for sulfur mustard will be equally applicable to dermal and eye exposure from Lewisite.

**PULMONARY IRRITANTS**

Many chemicals with pulmonary irritant properties have been proposed as potential military/terrorist weapons, but only two are discussed in this article: chlorine and phosgene. Both chlorine and phosgene were used during WWII, sometimes in combination. Both are gases that cause irritation in the lung. Chlorine, with relatively high water solubility, is readily scrubbed in the upper airway, whereas phosgene, with relatively low water solubility, penetrates deeper into the lung. Both agents release hydrochloric acid on reaction with water, and both produce capillary leak with pulmonary edema. These symptoms appear rapidly after chlorine exposure, whereas after phosgene exposure symptoms are often delayed for many hours. Chlorine is also a significant irritant to the skin and the eye. Phosgene, but not chlorine, is capable of reacting with nucleophilic groups (amino, hydroxyl, and sulfhydryl) in tissues, leading to irreversible tissue injury and decreased levels of antioxidants. This mechanism is thought to be responsible for much of the damage caused by phosgene. Chlorine is considered a likely agent for use in terrorist acts because of its ready availability; it is used widely in industry, and large quantities of it are regularly stored and shipped. In addition to military use, a large number of accidental releases of chlorine have occurred during transportation and workplace accidents.

There are no antidotes for exposure to chlorine and phosgene. Chlorine exposures of the skin and eye are easily treated with a water flush to remove the irritant hydrochloric acid. Some controversy exists about optimal treatment for inhalation injury with either of these agents. Basic supportive therapy with humidified oxygen and positive pressure ventilation are the mainstays of treatment. Numerous reports in both animals and humans have documented the apparent value of both oxygen and positive pressure, but there have been no controlled human trials. If bronchospasm develops, particularly in individuals with preexisting hyperactive airways, bronchodilators are recommended. There are no data specifically assessing the effectiveness of bronchodilators for chlorine- or phosgene-induced bronchospasm. Several case reports and case series have investigated the efficacy of nebulized sodium bicarbonate (3.5–4%) as an antidote in patients who have inhaled chlorine. This treatment appears to be safe and effective at relieving the discomfort associated with exposure to chlorine. However, none of the reports had a control group, and none assessed the effects on short-term or long-term pulmonary outcome.

A controlled study of chlorine inhalation in a sheep model, using nebulized 4% sodium bicarbonate as an antidote, showed improvement in respiratory function as measured by arterial blood gases but no improvement in lung pathology or survival in the treatment group. Corticosteroids have also been recommended on the basis of analogy with other inflammatory lung diseases. There are no human studies evaluate the efficacy of corticosteroids as a treatment for chlorine or phosgene inhalation injury. Several studies in animals have investigated the effects of steroids in chlorine inhalation models. Demnati et al. treated chlorine-exposed rats with dexamethasone 1 h after exposure. Recovery was more rapid in the treatment group as compared with the control group. In a pig model, Gunnarsson et al.
showed that there was a marked improvement in chlorine-related pulmonary symptoms in animals treated with beclomethasone as compared with controls.

Studies in animals to investigate antidotes to phosgene exposure have also demonstrated a reduction in both pulmonary edema and mortality rate with steroid administration, both pre-exposure and postexposure. On the other hand, Smith et al. failed to find any decrease in mortality or pulmonary edema in a porcine model employing treatments with either inhaled budesonide or intravenous methylprednisolone. On the basis of the presumed mechanism of action of phosgene, several other treatments have been tried in animal models. Intratracheal N-acetyl-L-cysteine, given after exposure in a perfused lung rabbit model, showed reduction in lung pathology. In a collection of both in situ and in vivo experiments, Sciuto and Hurt have also shown efficacy against phosgene-induced lung injury with the use of ibuprofen, aminophylline, and isoproterenol. Kennedy et al. have reported similar results. A large number of other substances have reportedly been tried for reducing phosgene-induced lung injury in animals and humans, but most have proven ineffective.

In summary, there are no published trials in humans to evaluate potential treatments for either chlorine or phosgene inhalation injury. Anecdotal reports and data from animal studies, as well as analogy to other inhalation injuries, strongly suggest that there would be a benefit from supportive treatment with humidified oxygen and positive pressure. Although there are conflicting data from animal studies with respect to the use of steroids, most of the studies have reported positive outcomes with this line of treatment. Data from animal studies suggest that anti-inflammatory and antioxidant drugs, such as ibuprofen and N-acetyl-L-cysteine, may have a role in treating phosgene inhalation injury. Data in humans are needed to adequately assess these treatments, and none can be routinely recommended on the basis of presently available data.

NERVE AGENTS

Nerve agents (NAs) are potent OPs with high potential for causing toxicity in humans after dermal or inhalation exposure. They were first discovered in Germany during the 1930s, as an outgrowth of research on OP insecticides. Many of these agents have been described; only four are discussed in this article: tabun (GA), sarin (GB), soman (GD), and VX. Although some of these agents were developed and manufactured by Germany before and during WWII, they were not used in that war. Reports indicate that they were probably used by Iraq against both the Kurds and Iran in the 1980s. Sarin was also used in at least two terrorist incidents in Japan during the 1990s. As with OP insecticides, these agents bind to, and are irreversible inhibitors of, cholinesterase enzymes. A recent analysis suggests that inhibition of acetylcholinesterase (AChE) accounts for >90% of the toxicity exhibited by these agents. Inhibition of AChE leads to accumulation of acetylcholine at the synapses. The bond between NA and enzyme is initially amenable to reversal, but it “ages” over time, becoming irreversible. The toxicology of these agents has been extensively studied in both animals and humans. The major difference in their toxicology relates to the time it takes to “age” the bond between agent and enzyme. Soman, in particular, ages within minutes, whereas the others age over hours (sarín, tabun) or days (VX). There is a very large body of literature related to toxic exposures of humans to OP insecticides. It is estimated that these widely used products poison several million people annually worldwide. Data on insecticidal OP poisoning in humans are a reasonable surrogate for the lack of data related to NA.

The major exposure routes for NA are inhalation and dermal exposure. All these agents are well absorbed by both routes, with rapid onset of symptoms, including respiratory failure and seizures. The traditional treatment includes, after decontamination, an anticholinergic agent to block acetylcholine receptor sites, an oxime to interact with and break the NA–enzyme bond (reactivation), and an anticonvulsant to prevent or treat seizures. Because of the major risk posed by these agents as terrorist weapons, much research has been done, and continues to be, on improved treatment agents and strategies. Because all NAs are water soluble, the usual recommendation for decontamination after a dermal exposure is removal of clothing and copious washing with soap and water or with water alone. Various military groups also use a variety of adsorbent materials. These materials are usually composed of activated charcoal and resins. Sodium or calcium hypochlorite solutions have also been recommended, if available. There are no published human studies assessing or comparing various methods of decontamination after exposure to an NA.

Although other anticholinergics have been tried, atropine is universally recommended and used. One small RCT in patients with OP poisoning compared atropine with glycopyrrolate, an anticholinergic with fewer CNS side effects than atropine. No significant differences were found between the two treatments; however, the power was low. Atropine has the advantages of being readily available, stable in solution over a wide temperature range, and readily absorbed after intramuscular injection. The military outfits in many countries supply atropine in auto-injectors (with or without added oxime and benzodiazepine) to troops who are at risk of facing chemical agents. Although atropine is usually administered intramuscularly or intravenously, a comparison study in humans has shown equivalent therapeutic and pharmacokinetic response when atropine is administered by inhalation. Atropine competes with acetylcholine for postsynaptic muscarinic receptors. It does not bind to nicotinic receptors but does cross the blood–brain barrier. It therefore prevents or treats respiratory and cardiac symptoms, and also some of the CNS symptoms, associated with cholinergic excess. Atropine does not reverse peripheral muscle weakness. There is no upper limit to the atropine dose in OP poisoning, with most authors recommending the resolution of respiratory symptoms as the end point. Excessive atropine can cause significant cardiac and CNS side effects. Dosing recommendations for atropine have been reviewed. There are no RCTs involving the use of atropine to treat OP poisoning, and such a study may no longer be ethically possible, because the efficacy of atropine is already universally accepted. There are many reports of atropine use in either NA or OP pesticide poisoning, with apparently favorable response with regard to cardiac, respiratory, and CNS symptoms. Dawson reviewed the animal data on the use of atropine, alone
or in combination with an oxime, in the treatment of poisoning with tabun, sarin, soman or VX. As pointed out by numerous authors, it is difficult to interpret data from animal studies in this area because of clear species differences. Most authorities are of the opinion that guinea pigs, rabbits, and primates are the best animal models for extrapolation to humans. In most studies in animals to investigate the effect of atropane alone, some degree of protective effect is shown. These effects are generally enhanced if atropine is given with an oxime. In contrast, oxime alone seems to have little protective effect. Human data, obtained from Iran and elsewhere, also suggest that atropine alone is sufficient treatment for exposure to any of the NAs. In summary, although there are no published RCTs with the use of atropine in NA poisoning, there are sufficient data from reported human experience, combined with data from animal studies, to reasonably conclude that it is an effective antidote for all kinds of OP poisoning, including NA poisoning.

Another antidote that is routinely used to treat NA poisoning is an oxime. Oximes, as reactivators of AChE, were first described by Wilson and Ginsburg in 1955. Since then, many additional oximes have been synthesized and tested in animals. Four oximes are available for use in humans: pralidoxime (2-PAM and P2S, available in the form of various salts), obidoxime (Toxogonin or LuH-6), trimedoxime (TMB-4), and HI-6 (asoxime). Pralidoxime (used in the United States and the United Kingdom) is a quaternary pyridinium salt. Obidoxime (used in much of Europe), trimedoxime, and HI-6 are bis-pyridinium salts. Being salts, none of these agents has significant penetration of the blood–brain barrier, with brain levels of these agents estimated to be 4–10% of plasma levels after administration.

There is considerable controversy over the efficacy of oximes in OP poisoning. It is clear, from in vitro and animal models, that efficacy is dependent on the particular oxime, the dose of the oxime (and perhaps the schedule of administration), the particular OP, the animal species, and probably pharmacogenetic differences that affect the metabolisms of both oxime and OP. This complexity leads to often contradictory and confusing results. The consensus of data indicates that all the available oximes are capable, in the right circumstances, of reactivating AChE to some degree. The question remains whether these effects, particularly with NA, are clinically significant. All the oximes available also have significant potential adverse side effects. This is particularly true of obidoxime, which is hepatotoxic in humans, an effect that frequently surfaces during clinical use and that has led to deaths of patients. There is a significant amount of human data regarding oxime usage, although most of these data are from case reports and case series related to insecticidal OP.

A number of recent reviews have assessed oxime use and efficacy in OP poisoning. Several published human studies were designed to assess oxime efficacy, all involving patients who had been poisoned with agricultural OP. These studies compared either the efficacies of atropane alone and atropane in combination with 2-PAM, or those of two different dosing regimens of 2-PAM coadministered with atropane. One study also had groups comparing the combination of pralidoxime and atropane with the combination of obidoxime and atropane. Peter et al. reviewed seven of the eight studies that investigated the efficacy of 2-PAM in combination with atropane as compared with that of atropane alone. Of the eight studies that investigated the efficacy of 2-PAM vs. therapy without oxime, three were blinded RCTs. The largest and most recent of these studies, by Eddleston et al. in 235 patients with OP poisoning, prospectively randomized the subjects to receive either atropane alone (control) or atropane in combination with 2-PAM (treatment). The study was double-blinded and used World Health Organization (WHO)-recommended doses of 2-PAM. The outcome measures were fatality rate, need for intubation, and enzyme reactivation as measured in terms of serial red blood cell AChE levels. The mortality rate was nonsignificantly higher in the treatment group (24.8 vs. 15.8%). The need for intubation was also similar in the two groups (21.5% in the treatment group vs. 21.1% in the control group). Serial AChE levels showed clear evidence of significant enzyme reactivation in the treatment group.

The first of two studies by Cherian et al. involved 110 patients and showed significantly higher rates of death and need for intubation in the 2-PAM group as compared with the group on atropane alone. The second study by Cherian et al., involving only 21 patients, showed no significant differences in mortality (1 patient in each group died), rates of ventilation, or days of intensive care unit stay. Although the 2-PAM dose used in the second Cherian study was larger than the one used in the first study, it still fell short of the WHO-recommended dose. The other nonrandomized studies of atropane, alone or in combination with 2-PAM, also failed to find any significant clinical advantage in the use of 2-PAM. Balali-Mood et al. used a three-armed study design that allowed for a comparison of 2-PAM and obidoxime, each coadministered with atropane. Although the numbers were small (22 patients with obidoxime and 8 with 2-PAM), the study suggested that 2-PAM was preferable to obidoxime because of a lower mortality rate. Respiratory complications were found to be significantly more likely in the oxime-treated groups. Two patients in the study died from presumed obidoxime hepatotoxicity.

Four studies have looked at high-dose vs. low-dose 2-PAM coadministered with atropane. In three of the four studies, high-dose 2-PAM yielded better outcomes, including lower death rates and less need for respiratory support. In the fourth study, the high-dose group showed a higher death rate and an increased rate of development of intermediate syndrome. In addition to the 2-PAM studies discussed here, some case series have been reported for obidoxime and HI-6.

It should be noted that none of the above data are in patients poisoned with NA. There have been several reports of individuals exposed to sarin or VX in various terrorist and homicidal events in Japan. Unfortunately, because few details of the treatment are available and most of the patients were mildly exposed, these reports shed little light on the question of the efficacy of oxime treatment to counteract NA poisoning. Sidell reported on the treatment of five patients with accidental occupational exposure to sarin and soman. Two of the patients, one exposed to sarin and the other to soman, received treatment with atropane and 2-PAM, and both survived. The other three patients had
In summary, recent data, particularly from three RCTs, have raised concerns about the clinical efficacy of oxime therapy in OP poisoning. Data from both animal and human studies clearly show that oximes can reactivate cholinesterase enzymes, but significant clinical effects appear to be absent. It is unclear why there is a disconnect between biochemical evidence of effect and clinical evidence of effect. Clearly, this is an area that urgently requires additional research. In the meantime, it seems prudent to consider the use of oximes to be a therapeutic option but not a requirement for OP or NA poisoning. It is also possible that the development of new, perhaps more effective, oxime derivatives will resolve this issue.

The third antidote usually used in OP poisoning is an anticonvulsant, given that cholinesterase inhibitors frequently induce multicentric seizures. Data from animal studies suggest that seizure activity is initially mediated by cholinergic mechanisms. If this is left uncontrolled during the initial stages, other neurotransmitter systems begin to participate in the generalized seizure activity, and eventually prolonged seizure activity becomes cholinergic independent. This proposed model explains the early effect of anticholinergics, such as atropine, in controlling OP-induced seizure activity. If seizures are not controlled very shortly after onset, they become increasingly refractory to atropine therapy. During the latter stages of therapy, benzodiazepines have been shown to be the treatment of choice, with many other anticonvulsants showing little or no effect. McDonough et al. have evaluated the relative efficacy of six benzodiazepines against soman-induced seizures in a guinea pig model. Midazolam was the most potent and rapidly acting drug of the group, which also included diazepam, lorazepam, and clonazepam. Midazolam has been shown to have rapid and equivalent activity through the intramuscular and intranasal routes in the guinea pig model of soman-induced seizures, whereas the sublingual route gave significantly slower results in this model. Midazolam has also been shown to act rapidly through the intravenous route in a pig model of paraoxon-induced seizures. Control of seizures is essential to

<table>
<thead>
<tr>
<th>Agent</th>
<th>Antidote/treatment</th>
<th>Strength of evidence</th>
<th>Data source</th>
<th>Reference(s)</th>
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<td>Cyanide</td>
<td>Nitrite + sodium thiosulfate</td>
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<td>Fresh-frozen plasma/bioscavengers</td>
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BAL, British anti-Lewisite; 4-DMP, 4-dimethylaminophenol; DMPS, 2,3-dimercaptop-1-propanesulfonic acid; DMSA, meso-2,3-dimercaptosuccinic acid; NAC, N-acetyl-L-cysteine.

*Methodologies and policies from the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on Practice Guidelines. Methodology manual for ACCF/AHA guidelines writing committees. Dallas, TX: ACCF and AHA, January 2010. Letters A–C designate the levels of available evidence, with A being extensive and C being very limited. Numbers I–III designate the strength of recommendation, with I being a strong recommendation to use and III being a recommendation not to use.
protecting against brain injury in NA poisoning. In summary, there are no RCTs of anticonvulsant therapy in humans with NA or OP poisoning. There are adequate data from animal studies to conclude that all benzodiazepines are likely to be effective in controlling NA-induced seizures and that midazolam may be the preferred drug of this class. There also appear to be adequate data from animal studies to support the value of anticholinergic agents, such as atropine, in the control of NA-induced seizures; however, this has no direct relevance because an anticholinergic agent is universally used in NA/OP poisoning for other reasons.

Several other agents and procedures have been used, either clinically or experimentally, in patients with OP poisoning. Only one human trial has evaluated the effectiveness of sodium bicarbonate in treating patients with OP poisoning. In an RCT, 26 patients with moderate to severe OP poisoning received sodium bicarbonate (5–6 mEq/kg/day administered intravenously) in addition to atropine and 2-PAM. Twenty-seven control patients received atropine and 2-PAM without bicarbonate. Several outcome measures were assessed, but only atropine utilization and length of hospital stay were statistically different between the groups, both favoring the bicarbonate-treated group. Data from animal and human studies related to bicarbonate treatment in OP poisoning have been reviewed.

Hemodialytic techniques have also been advocated for treating OP poisoning. An early uncontrolled retrospective study that reported on the use of hemoperfusion in 10 patients concluded that the technique was of no value in improving outcomes. Two recent studies have shown conflicting results with hemoperfusion. Altintop et al. reported on 25 patients with severe OP poisoning who received hemoperfusion and 27 mildly poisoned patients who did not receive hemoperfusion. All the patients received atropine, 2-PAM, and other traditional supportive measures. There were seven deaths in the hemoperfused group and none in the mildly poisoned group. AChE levels were measured in some patients and showed an increase with hemoperfusion. It is difficult to reach any conclusions from this uncontrolled study, although the authors concluded that hemoperfusion may be useful in severe OP poisoning. In another nonrandomized study, Peng et al. reported on a group of 108 patients with severe dichlorvos poisoning, 67 of whom received hemoperfusion. Hemoperfusion was associated with significantly decreased mortality (7.5 vs. 34.1%), decreased need for ventilation (13.4 vs. 36.6%), shortened intensive care unit stays (4.0 vs. 6.0 days), and shortened length of coma (9 vs. 16 h). Three case reports have described favorable outcomes in patients treated with a combination of hemodialysis and hemoperfusion for poisoning with VX, parathion, and dimethoate. Several additional case reports have reported variable results with charcoal hemoperfusion.

One case report describes the use of fresh frozen plasma (FFP) and plasmapheresis in an attempt at bioscavenging in a patient with OP poisoning and sepsis. The authors of the case study speculated that the butyrylcholinesterase in FFP may be the bioscavenger, although other data suggest that this may not be so. In a prospective, partially randomized study of 33 patients with OP poisoning admitted to an intensive care unit, 12 patients received FFP; 10 of these received the treatment from day 2, and the other 2 patients received it only after the onset of intermediate syndrome, a delayed neuromuscular deficit that occurs after significant OP poisoning. All the patients also received standard therapy with atropine and 2-PAM, except one patient in each group who received atropine alone. FFP was found to increase butyrylcholinesterase levels. Intermediate syndrome occurred in 28.6% of the control patients but in 0% of the patients who initially received FFP. There were five deaths on the whole, three in the control group and two in the treatment group; the latter two patients had received FFP treatment only after they developed intermediate syndrome.

Considerable research into the development of other bioscavengers is under way. The candidate that is in the most advanced stage of development and has completed phase I trials is a recombinant form of butyrylcholinesterase produced in transgenic goats. A study of human butyrylcholinesterase in pigs poisoned with sarin showed excellent results consistent with effective scavenging by the drug. Other enzymes that either hydrolyze or bind NA are under study. Lipid emulsions, combined with extracorporeal removal, have also been suggested but not tested.

A single, small, human prospective RCT has also investigated the effect of magnesium in 45 patients with OP poisoning. All the patients received atropine and either 2-PAM or obidoxime. In addition, every fourth patient received a 4 g. intravenous infusion of magnesium sulfate over the first 24 h. The death rate (14.7 vs. 0%) and length of hospitalization (5.0 vs. 2.9 days) were both significantly lower in the magnesium-treated group. A previous report of the use of magnesium sulfate in four patients did not document any significant clinical response.

**SUMMARY**

There is currently a great deal of concern about chemical weapons because of their perceived potential use by terrorist groups. Unlike nuclear or biological agents, many chemical agents are relatively easy to either make or acquire from commercial sources. Table 2 summarizes the evidence available in the published literature regarding the effectiveness of antidotes and treatments for exposure to chemical warfare agents. The strength of evidence is categorized using the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines system. This review highlights the facts that not much is known about potential antidotes for these various agents and that much more research is needed. The current use of antidotes is based on very poor evidence relying primarily on animal models, data from poorly controlled studies in humans, and analogy to similar conditions. Recent concise and critical reviews of specific antidotes represent a step forward in this area, as do attempts to improve the development of evidence-based medicine in toxicology in general.

**SUPPLEMENTARY MATERIAL** is linked to the online version of the paper at http://www.nature.com/cpt

**CONFLICT OF INTEREST**

The authors declared no conflict of interest.

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