

Treating Exposure to Chemical Warfare Agents: Implications for Health Care Providers and Community Emergency Planning

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Current treatment protocols for exposure to nerve and vesicant agents found in the U.S. stockpile of unitary chemical weapons are summarized, and the toxicities of available antidotes are evaluated. The status of the most promising of the new nerve agent antidotes is reviewed. In the U.S., atropine and pralidoxime compose the only approved antidote regimen for organophosphate nerve agent poisoning. Diazepam may also be used if necessary to control convulsions. To avoid death, administration must occur within minutes of substantial exposure together with immediate decontamination. Continuous observation and repeated administration of antidotes are necessary as symptoms warrant. Available antidotes do not necessarily prevent respiratory failure or incapacitation. The toxicity of the antidotes themselves and the individualized nature of medical care preclude recommending that autoinjectors be distributed to the general public. In addition, precautionary administration of protective drugs to the general population would not be feasible or desirable.

No antidote exists for poisoning by the vesicant sulfur mustard (H, HD, HT); effective intervention can only be accomplished by rapid decontamination followed by palliative treatment of symptoms. British anti-Lewisite (BAL) (2,3-dimercapto-1-propanol) is the antidote of choice for treatment of exposure to Lewisite, another potent vesicant. Experimental water-soluble BAL analogues have been developed that are less toxic than BAL. Treatment protocols for each antidote are summarized in tabular form for use by health care providers.

Introduction

The U.S. stockpile of aging lethal unitary chemical weapons and agents is currently scheduled for destruction by April 30, 1997, under the Department of Defense Authorization Acts (PL 99-145 and PL 100-456). Unitary weapons contain lethal agents at the time of assembly, in contrast to binary weapons containing agent precursors that mix upon firing and react to form lethal agents. Thus, the deteriorating unitary weapons stockpile poses a threat in storage as well as in handling during disposal. The stockpiled chemical agents include the organophosphate nerve agents GA (tabun; *N,N*-dimethyl phosphoramidocyanidate, ethyl ester), GB (sarin; methylphosphonofluoridate isopropyl ester), and VX [*S*-(diisopropylaminoethyl) methylphosphonothiolate *o*-ethyl ester] and the vesicant (blister) agents H/HD [sulfur mustard; *bis*(2-chloroethyl) sulfide], HT: 60% HD and 40% T or *bis*[2(2-chloroethylthio)ethyl] ether, and Lewisite [dichloro(2-chlorovinyl)arsine]. These agents were specifically designed to cause incapacitation or death in military use and are quite effective due to their high toxicities at low doses.

The unitary stockpile is housed at eight locations in the continental U.S. in the form of various weapons (bombs,

cartridges, mines, projectiles, rockets), spray tanks, and ton containers (Fig. 1). Two locations, Aberdeen Proving Ground (near Edgewood, Maryland) and Pueblo Depot Activity (near Pueblo, Colorado) store only mustard agent, while the rest stockpile both nerve and blister agents. Agents GB and VX compose most of the nerve agent inventory; a small amount of GA is housed only at Tooele Army Depot near Salt Lake City, Utah.

An analysis of the available antidotes for each nerve and blister agent in the stockpile was performed as a part of evaluating the options of on-site destruction versus transport to a regional disposal facility (*1*). Current decontamination and treatment protocols, antidote toxicities, and the status of recently developed antidotes were evaluated. The study objectives were to compile what is known about antidotes and treatment protocols and to make this information available for evaluation of the risks entailed in various stockpile destruction options and for use by health professionals in community emergency planning.

The essential nature of emergency planning was highlighted in the Final Programmatic Environmental Impact Statement (*1*) for the Chemical Stockpile Disposal Program (CSDP); the probabilities of individual accidents with off-site consequences during the disposal program range from 1×10^{-4} to 1×10^{-10} for the entire stockpile (*1,2*). Thus, the probability of accidents occurring is low but considered credible (i.e., requiring emergency preparedness at prob

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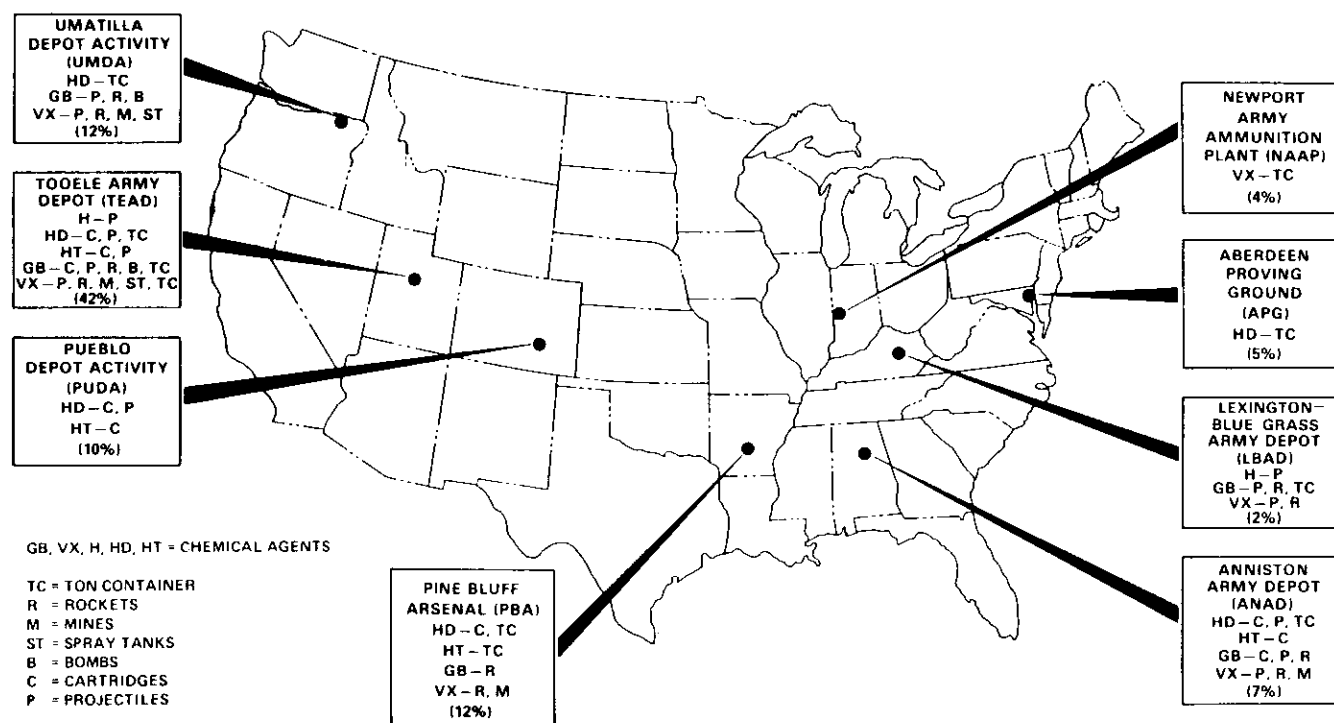


FIGURE 1. Unitary chemical weapons stockpile distribution throughout the U.S. (small quantities of GA and Lewisite are also stored at Tooele Army Depot).

abilities $\geq 10^{-8}$ (3). In the event of an accident during the CSDP, the average maximum number of fatalities is estimated to be over 500, ranging from 1 to more than 1400 under conservative most likely weather conditions (3). (Average maximum fatalities is the average of the maximum potential fatalities within 20 km for all accidents at all sites involving all munitions types for both the on-site disposal and continued storage options, since storage will continue until stockpile destruction is complete.) Under worst-case meteorological conditions, the potential maximum number of fatalities for credible accidents during the CSDP is estimated to range from 1 to 5400, where the wind carries the plume over the area of largest population density (1). It should be noted that the estimated fatalities from credible accidents for the continued storage option are significantly higher than those for on-site disposal for all sites but one (1).

These large numbers of estimated fatalities stem from the fact that several sites have significant populations so near that to alert and evacuate or protect them once a release was detected may be difficult (3). For example, three sites are moderately populated (between 26,000 and 41,000 persons within 10 km), and three more have populations of 4,000 to 7,000 within that distance (1). The 10-km perimeter is considered the immediate response zone, with less than a 1-hr response time for most accident scenarios (3).

Hence, inadvertent release could have a catastrophic effect on the surrounding civilian population. The difficulty of preventing fatalities is heightened by the necessity for emergency and medical personnel to work in full protective gear while treating and decontaminating victims and decontaminating all equipment used on exposed patients (4). Such difficulties may be exacerbated by the need to

evacuate medical facilities should they be in the contaminated area; access to such facilities would be impossible for an indefinite period thereafter (5).

Furthermore, the widespread possession and the recent documented use of mustard, cyanide gas, and probably a nerve agent by Iraq against civilian (6) as well as military targets in Iran has raised fears that such use may expand to other regional conflicts (7). The potential for use by terrorists against civilian populations also exists. Such developments add weight to the need for a heightened awareness among civilian medical personnel and emergency planners of the mode of action of chemical warfare agents, the nature of available antidotes, and treatment protocols.

Nerve Agent Exposure

The nerve agents in the unitary weapons stockpile are organophosphate esters chemically similar to organophosphate pesticides but with higher acute toxicity. For example, while the rat dermal median lethal dose (LD_{50} , mg/kg) is only 0.1 for VX and 2.5 for GB, it is 6.8 for parathion, 4000 for sevin, and 4400 for malathion (5). Nerve agents are absorbed by several routes and are hazardous in vapor, liquid, or aerosol form. They are colorless, generally odorless, tasteless, and nonirritating to the skin, so exposure to a lethal dose can occur without being perceived by the individual. These agents act by inhibiting the enzyme acetylcholinesterase (AChE), which breaks down the neurotransmitter acetylcholine (ACh) and prevents its excessive accumulation at nerve endings. The symptoms resulting from nerve agent exposure are primarily the consequence of accumulation of excess ACh at nerve junctions where ordinarily small amounts of ACh are needed for impulse

transmission. Excess build-up of ACh within portions of the nervous system controlling smooth muscle, cardiac muscle, and endocrine-exocrine functions can cause some or all of the following symptoms: drooling, increased bronchial secretions, bronchoconstriction, miosis, excessive sweating, vomiting, diarrhea, abdominal cramping, involuntary urination, and cardiac arrhythmias (8). Within the central nervous system, ACh accumulation can result in headache, anxiety, confusion, restlessness, giddiness, EEG changes, or even convulsions and coma, depending on agent and dosage (8). When skeletal muscles are affected by ACh accumulation, there can be a generalized weakness, twitching, and cramping. Respiratory failure is the immediate cause of death from lethal doses, and is the result of excess ACh not only in the peripheral nervous system (neuromuscular blocks, increased lung secretions) but also in the central nervous system (depression of the respiratory center). Dunn and Sidell (9) describe variations in nerve agent effects with different routes and degrees of exposure.

The nerve agents also have pharmacologic effects other than AChE binding (noncholinergic effects), but the acute toxic effects, especially those involved in respiratory failure, are generally accepted as being cholinergic. A detailed review of nerve agent toxicity is found in the Chemical Stockpile Disposal Program Final Programmatic Environmental Impact Statement (1) and is summarized by Watson et al. (5) and Carnes and Watson (2).

The two main nerve-agent constituents of the stockpile differ markedly in their volatility and consequent potential health effects. VX, the most potent of the stockpile agents, is the least volatile (10.5 mg/m³ saturated air concentration at 25° C) and would not disperse as widely as GB, a highly volatile agent (22 × 10⁴ mg/m³ saturated air concentration at 25° C) (2). VX, unlike GB, could therefore persist in the environment and on the skin long after an exposure.

Decontamination

If exposure has resulted in skin or clothing contamination, the individual must be removed from the affected area and immediately decontaminated. This should be done by trained and protected emergency personnel, taking utmost care to avoid self-contamination. Procedures are detailed for battlefield situations by Sidell (4,10) and would need adaptation for civilian applications. Decontamination can be effected by removing all contaminated clothing and blotting (not swabbing or wiping) the skin with an alkaline solution on wipes from the M258A1 Army Decontamination kit or with resin-based wipes from the M291 kit (11) followed by 0.5% sodium hypochlorite (HTH) (a 1:9 dilution of household bleach). If these kits are not on hand, decontamination can be effected by using 0.5% HTH (12) or most any alkaline substance (4,10). In the absence of an M291 kit, washing with copious amounts of water or weak alkaline solution will remove the nerve agent but will not break it down. Thus, the contaminated washwater must be contained and disposed of. The adequacy of decontamination can be assessed by using ABC-M8VGH detection paper after thorough washing and then washing again as necessary

(4,10). Unless the exposure is known to be only to nerve agent, any bleach or alkaline decontaminant must be removed before using the detection paper as it will react to bleach by turning red, a positive reaction for mustard agent.

Nerve Agent Antidotes in Current Use

The choice of appropriate treatment for nerve agent poisoning depends on the agent and the extent and route(s) of exposure. Very mild exposure to nerve agent vapor may necessitate only decontamination and observation; severe exposure to vapor or liquid requires immediate decontamination, administration of antidotes, establishment of artificial respiration (13,14), continuous monitoring for at least 24 hr in order to tailor the antidote dose to the individual victim's clinical condition, and intensive supportive therapy over hours or days to maintain life.

Immediate care is vital to prevent death from respiratory failure, which can occur within minutes or even seconds in cases of massive inhalation exposure (15). Monitoring of the AChE level provides retrospective confirmation of poisoning but is not likely to be helpful in managing the patient during the acute phase. Prompt attention is also necessary because the agent-AChE complex becomes resistant in various degrees to reactivation by oxime-type antidotes within minutes to a few hours, depending on the agent. The standard antidotes available clinically in the U.S. are atropine (an anticholinergic drug) and pralidoxime (Protopam or 2-PAM-Cl). In addition, central nervous system (CNS)-active drugs such as diazepam (Valium) may be used if convulsions occur.

Atropine. Atropine is used to antagonize the excess ACh that accumulates at nerve endings in the absence of functional AChE. It counters the bronchoconstriction and bronchosecretions that interfere with breathing or support by a respirator. Atropine also opposes the agent's toxic effects of nausea, vomiting, and diarrhea. It partially relieves the CNS respiratory depression but cannot reverse respiratory muscle paralysis (13,16).

Therapy for nerve agents is similar to that for organophosphate pesticides but usually requires higher initial atropine dosage and more frequent administration in the first several hours after exposure. However, it does not usually require as prolonged administration of atropine (Table 1) (4,15,17; F. R. Sidell, personal communication). Sidell (4,10,15) recommends 2 to 8 mg atropine intramuscularly (IM) or intravenously (IV), depending on the severity of symptoms. Injections should be given every 3 to 8 min or longer until decreased lung secretions and pulmonary resistance are seen. If the victim experiences only mild breathing difficulties or mild gastrointestinal distress, an initial atropine dose of 2 mg IM may suffice (4,10). In one case of accidental GB inhalation, initial injection of 4 mg atropine (2 mg IV + 2 mg IM) was followed by several 2-mg (IV except for one IM) doses over the next 2 hr. Pralidoxime was also required (18). Limited experience with nerve agent casualties indicates that 10 to 20 mg cumulative doses in the first 2 to 3 hr usually provides adequate control of symptoms (9). For organophosphate pesticide poisoning in children, Haddad

Table 1. Nerve agent antidote summary: actions, dosages, side effects/overdose symptoms.

Antidote/action	Dose	Overdose symptoms, management ^a
<p>Atropine (di-hyoscyamine)</p> <p>Anticholinergic alkaloid: used to block effects of parasympathetic nerve stimulation. Prepared from powdered roots of <i>Atropa belladonna</i> and <i>Datura stramonium</i>. In massive doses, used to treat AChE poisoning and to manage certain psychiatric states.</p> <p>Relieves smooth muscle constriction in lung and GI tract and reduces glandular paralysis (cleans up respiratory tract secretions).^b</p> <p>Toxicity rating 5, extremely toxic. [Probable oral lethal dose in humans of 5–50 mg/kg, or 7 drops to 1 teaspoon for 150-lb (70-kg) person].</p>	<p>Adult: 2–4 mg or more of atropine sulfate IM or IV. Full atropinization maintained at 2-mg doses every 3 to 8 min for several hours.</p> <p>Child: initial dose, 0.05 mg/kg. Maintenance doses for child range from 0.02 to 0.05 mg/kg.</p> <p>Mean lethal dose unknown (recovery after ingestion of 1000 mg documented); lethal estimate of 10 mg, although recovery documented at 100-mg dose in many adults; children more susceptible.</p> <p>For all: provide atropine until signs of atropinization occur (dry mouth and dry lungs); use until signs of improvement are seen; taper off dose.^c</p>	<p>Symptoms</p> <p>Dryness of mucous membranes, burning pain in throat, difficulty in swallowing, and intense thirst.</p> <p>Skin hot, dry, flushed. Rash over face, neck, and upper trunk, especially in infants and children. Peeling of skin may follow.</p> <p>Exceptionally high fever.</p> <p>Sinus tachycardia (rapid heart beat), palpitations, elevated blood pressure.</p> <p>Uncommonly: nausea, vomiting, and abdominal distension in infants, urinary urgency and hesitancy; inability to void.</p> <p>Restlessness, fatigue, excitement and confusion, progressing to mania and delirium, which may persist for hours or days. Hallucinations, particularly of visual type. Patients may exhibit self-destructive acts.</p> <p>Management</p> <p>Treat symptoms with physostigmine salicylate. Onset of symptoms within 15–30 min, maximum effects at 2–3 hr and recovery within 12 hr.</p>
<p>2-PAM-Cl (protopam chloride; 2-pyridine aldoxime methyl chloride; pralidoxime)</p> <p>Treat poisoning due to organophosphate insecticides and nerve gases; anticholinesterase antagonist. Effective when given with atropine.^a</p> <p>Acts by removing organophosphate from cholinesterase and restoring normal control of skeletal muscle contraction (relieves twitching and paralysis).^b</p>	<p>Adult: 1–2 g in 100 mL saline IV over 15–30 min for initial dose. Second dose after 1 hr if symptoms indicate.</p> <p>Children: initial dose of 15–25 mg/kg, followed by second after 1 hr if symptoms indicate.^d</p> <p>Infants: try 15 mg/kg.^d</p> <p>Less effective after aging (when bond between organophosphate and cholinesterase becomes irreversible). Substantial aging occurs within 5 hr for GB.^b</p>	<p>Symptoms</p> <p>Rapid and possibly dangerous rise in blood pressure.^d</p> <p>Temporary rapid heart beat (tachycardia).</p> <p>Mild weakness, dizziness.</p> <p>Blurred or double vision.</p> <p>Management</p> <p>Usually well tolerated with careful (slow) administration.</p>

^aFrom Gosselin et al. (17).

^bFrom Sidell (4,10).

^cFrom Sidell (15).

^dF. R. Sidell, personal communication.

and Winchester (19) recommend 0.05 mg/kg atropine IV, followed by maintenance doses of 0.02 to 0.05 mg/kg as needed. In cases of nerve agent exposure by vapor or on the skin, atropine can be administered quickly to adults from the armed forces MARK I Nerve Agent Antidote Kit if available. One kit provides one autoinjector containing 2 mg of atropine citrate and another containing 600 mg of pralidoxime chloride (9).



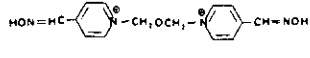
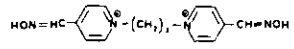
Atropine itself is highly toxic, with a rating of about 5 on a scale of 1 to 6, 6 being most toxic; the probable oral lethal dose for humans at this rating is given as 5 to 50 mg/kg [7 drops to 1 teaspoon for a 150-lb (70-kg) person] by Gosselin et al. (17). This antidote must therefore be used with caution and only with sure knowledge that nerve agent exposure has already occurred. This precaution is of particular importance with regard to children, the elderly, or debilitated individuals. In the absence of exposure, a 2-mg dose to an older person might result in "a greater degree of mental disturbance, including delirium, and the rapid heart rate might cause heart damage or precipitate an arrhythmia" (19). The major consequences of atropine overdosage are listed in Table 1. However, in cases of severe organophos-

phate exposure, by far the main treatment error has been atropine underdosage, rather than overdosage, because of the large doses required (17). Rapid administration of atropine to a cyanotic person may be dangerous, as Krop and Kunkel (20) occasionally observed fatal ventricular fibrillation in anoxic dogs and cats that they attributed to atropine given after GB exposure. However, in nerve agent poisoning it may not be possible to correct anoxia prior to giving atropine because of the intense bronchoconstriction, heavy bronchorecretion, and even lockjaw (trismus) that are characteristic of severe poisoning (17). In such cases, atropine administration may be necessary to relieve these symptoms so that respiration may be restored.

Monitoring of body temperature may also be indicated, particularly in infants and children, because atropine can cause exceptionally high fever (17). This may or may not be a problem in human cases of nerve agent exposure because nerve agents induce hypothermia in rodents (21). Hypothermia has apparently been noted in humans in a few cases of severe organophosphate pesticide exposure (21).

Pralidoxime. In a clear case of nerve agent exposure and with established symptoms beyond miosis (pinpoint

Table 2. Older oximes: nomenclature and abbreviations.

Trivial name	Abbreviation or trade name	Chemical name	Structure ^a
Pralidoxime chloride	2-PAM-Cl	Pyridine-2-aldoxime methyl chloride	 Cl ⁻
Pralidoxime methane sulfonate	P ₂ S	<i>N</i> -methyl-2-pyridiniumaldoxime methanesulfonate	 CH ₃ SO ₄ ⁻
Obidoxime	Toxogonin	bis[(4-Hydroxyiminomethyl)-pyridine-1-methyl]-ether dichloride	 2Cl ⁻
Trimedoxime	TMB ₄	<i>N,N'</i> -Trimethylene bis(pyridium-4-aldoxime) dichloride (or dibromide)	 2Cl ⁻

^aAdapted from Stares (13).

pupils) or tearing, a second antidote should be administered to complement the actions of atropine. Pralidoxime chloride is currently the only oxime antidote approved by the U.S. Food and Drug Administration (FDA) for clinical use in organophosphate poisoning. Its active oxime group, RCH=NOH, dissociates the nerve agent moiety from the AChE molecule, reactivating the enzyme and gradually restoring normal muscle function. The major effect of oximes is to restore skeletal muscle function; pralidoxime has little or no CNS effect, possibly because it does not seem to cross the blood-brain barrier readily (16). Common names, abbreviations, chemical names, and structures of pralidoxime chloride, pralidoxime methane sulfonate (P₂S), and two other oximes are displayed in Table 2 (13). As listed in Table 1, the usual adult dosage of pralidoxime consists of 1 to 2 g for a 70-kg person (14–28 mg/kg) IV in 100 to 150 mL of saline given slowly over 15 to 30 min (17,22). Blood pressure should be monitored carefully during the infusion. The initial dose may be followed by two or three periodic maintenance doses over a period of not more than 48 hr if muscle weakness persists and if the initial dose proves beneficial (23) or for as long as it appears to be of help. A suggested initial dose for children is 15 to 25 mg/kg according to F. R. Sidell (personal communication). Barr (22) recommends 25 mg/kg. No data are available on which to base a dose for infants, but Sidell recommends an initial dose of 15 mg/kg.

The limits on oxime use result both from the aging of poisoned AChE and from the toxicity of the oxime (23). Aging of agent-bound enzyme is thought to result from the loss of an alkyl or alkoxy group from the nerve agent moiety (16). The remaining enzyme-modified nerve agent complex is more stable and is resistant to reactivation by oximes or similar antidotes. The rate and extent of aging vary with the nerve agent in question. In humans, aging is substantial (50 to 60%) within 5 to 6 hr after GB exposure but less extensive (approximately 40%) even 48 hr after VX exposure (24).

Because of the AChE aging problem, prompt administration of an oxime antidote is essential and can be facilitated if nerve agent antidote kits are available to emergency medical personnel and to the workers involved in decommissioning nerve agent stockpiles. They can be used for self-

Table 3. Acute toxicity of 2-PAM-Cl and two H-oximes in four species.^a

Species	Route of injection	LD ₅₀ , mg/kg ± SE		
		2-PAM-Cl	HI-6	HGG-12
Mouse	IP	162 ± 4	670 ± 44	177 ± 9
Rat	IM	206 ± 3	860 ± 28	1179 ± 36
Guinea pig	IM	184 ± 2	500 ± 14	281 ± 4
Dog	IM	75 ± 2	350 ± 10	60 ± 4

^aAdapted from Boskovic et al. (26).

administration or administration by another.

Because pralidoxime itself is toxic, it must be used with caution. The patient must be monitored closely for hypertension when the drug is given IV because rapid infusion will produce a marked and potentially dangerous rise in blood pressure, as well as double vision, nausea, and vomiting (15). Mild weakness, dizziness, blurred vision, double vision (diplopia), and temporary rapid heartbeat have often been seen in normal subjects given doses as low as 0.5 g. At higher than therapeutic doses, pralidoxime can inhibit AChE and block neuromuscular transmission (16,23,25).

According to Sidell (15), there has been little use of this drug in children or elderly persons. Because these groups are generally more sensitive to drugs, it may be expected that these side effects might be more severe or be seen at lower doses in these populations.

LD₅₀ values for pralidoxime and two other oximes in four species are compared and presented in Table 3 (26). This oxime is substantially more toxic to dogs than to any of the three rodent species tested. It is of interest to note that the LD₅₀ for dogs (75 mg/kg) is not much greater than the therapeutic dose range (15–30 mg/kg) in humans. Calesnick et al. (27) studied the toxicity of pralidoxime, its methane sulfonate salt (P₂S), and trimedoxime (TMB₄) in human subjects. Of the three, pralidoxime was least toxic, P₂S somewhat more toxic, and TMB₄ most toxic, especially when given orally over extended periods of time rather than in a single dose.

Therapy for CNS Effects

In addition to the use of atropine and pralidoxime, therapy for other CNS effects may be needed. McLeod (28) cites

evidence for extensive brain lesions produced in experimental animals by GB and attributes it to seizure activity that kills neurons. Anticonvulsants such as diazepam have been used effectively in some experimental animals (29–31). On the basis of increased animal survival, diazepam is a part of the nerve agent treatment regimen adopted by the U.S. and the U.K. for military service use (9,32). Other CNS effects have been noted in clinical situations after the acute phase of poisoning has passed. Scopolamine, a compound related to atropine, has been useful in relieving nonlethal but disagreeable and potentially disabling psychological side effects of nerve agent exposure. A patient who had experienced a severe exposure to GD (soman; pinacoyl methyl phosphofluoridate) (a nerve agent chemically related to GA and GB, but not part of the stockpile of unitary weapons) suffered from temporary depression, bad dreams, decreased alertness, and disturbed sleep patterns during the recovery period after atropine and pralidoxime treatment (18). Administration of scopolamine hydrobromide produced a marked improvement in mental function (18). Very severe acute organophosphate pesticide exposure or chronic exposures have resulted in abnormal EEG patterns and a variety of neuropsychiatric symptoms varying in severity from anxiety to hallucinations (17). Thus, the treatment of nerve agent poisoning may require substances whose CNS activity can counteract deleterious effects not adequately opposed by atropine and pralidoxime. Clearly, these treatment agents are not needed until the acute effects of exposure have subsided and any psychological side effects have appeared.

Newer Oximes

A search has continued for an oxime or related compound that would combine high effectiveness (33,34) against all the nerve agents with low toxicity (35) and good chemical stability. To date, no ideal compound has been identified, although several promising substances have emerged.

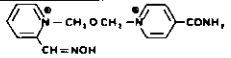
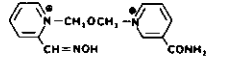
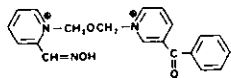
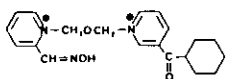
A so-called H-series of oximes has been synthesized in the laboratory of Inge Hagedorn of the University of Freiburg in West Germany. Of these, HI-6 and HS-6 appear to be among the most effective and least toxic. In addition, HGG-42 and HGG-12 have shown promise. The structures of these oximes are illustrated in Table 4 (34).

Toxicity values for HI-6 and HGG-12 in mice, rats, guinea pigs, and dogs are compared in Table 3 with those for pralidoxime (26). Interestingly, the H-oximes are also more toxic in dogs than rodents, as noted earlier for pralidoxime. HI-6 appears to be well tolerated by healthy human volunteers (36). Overall, HI-6 is a promising candidate to replace pralidoxime, but is not expected to be available during the lifetime of the CSDP since clinical testing and FDA approval would be necessary for its use.

Pretreatment Regimens

In addition to the development of new oximes, combinations of other therapeutic agents with atropine and oximes have been examined. A promising approach has been to

Table 4. Newer oximes: nomenclature and structure.^a

Abbreviation	Structure	
HI-6		2Cl ⁻
HS-6		2Cl ⁻
HGG-12		2H ₂ O
HGG-42		2H ₂ O

^aAdapted from Lenz and Maxwell (34).

pretreat with carbamate compounds that are, themselves, anticholinesterases. The carbamate protects a fraction of AChE from blockage by nerve agent; the carbamate moiety then spontaneously hydrolyzes from the AChE molecule within a matter of hours.

Pretreatment is a part of the approach adopted recently by the United States and the United Kingdom for those military personnel considered at risk of nerve agent attack. The U.K. plans to use a combination of P₂S, atropine, and diazepam together with pyridostigmine (a carbamate) pretreatment (32,37). The U.S. will distribute pyridostigmine bromide tablets (30 mg every 8 hr) to combat units equipped with atropine and pralidoxime autoinjectors; diazepam will also be available via aid men (9). Pretreatment with pyridostigmine substantially increases the protective effects of atropine and P₂S against the lethal effects of GB and VX in guinea pigs, and the addition of diazepam as a therapeutic agent further enhances survival (32). The improvement in protection afforded guinea pigs by adding pyridostigmine pretreatment and diazepam as supportive therapy in addition to atropine and oximes is compared in Table 5 with the values for atropine and oxime alone (31). The basis for comparison is the protective ratio, that is, the ratio of LD₅₀ with treatment to LD₅₀ without treatment. The higher the value, the more protection is afforded by the therapeutic combination.

A related carbamate, physostigmine, has been shown to protect animals against not only nerve agent lethality, but also incapacitation. Physostigmine (a compound that enters the CNS more readily than pyridostigmine), when used together with atropine (an anticholinergic) as a pretreatment, gave better protection in guinea pigs than did pyridostigmine alone or in combination with atropine against both death and incapacitation by GB (37). In both cases, post-poisoning therapy consisted of atropine, P₂S, and diazepam. Physostigmine, like pyridostigmine, is widely used clinically for the treatment of myasthenia gravis (16). However, it has not been approved for use in humans as a pretreatment against nerve agent exposure since it causes undesirable side effects at the necessary doses (9).

Other current and promising research directions aimed at countering nerve agent exposure in humans include pre-exposure loading of animals with an excess of circulating

Table 5. Therapeutic value of oxime antidotes against GA, GB, and VX with pyridostigmine pretreatment in guinea pigs.^a

Antidote	Dose, mg/kg	Protective ratio ^b					
		GA		GB		VX	
		Without ^c	With ^c	Without	With	Without	With
No oxime	0	1.3	11	<3	11	<3	15
P ₂ S	30	2.5	34	38	45	25	69
HS-6	47	2.6	73	35	57	9.6	82
HI-6	49	2.2	34	76	110	66	68
HGG-12	81	3.7	68	12	54	5.1	55
HGG-42	82	—	12	—	40	—	31
TMB ₄	46	13	76	46	220	40	310
Toxogonin	47	19	—	59	380	58	410

^a Adapted from Inns and Leadbeater (31).

^b Protective ratio = LD₅₀ with treatment / LD₅₀ without treatment.

^c Without, without pyridostigmine and diazepam; with, with these compounds; pyridostigmine (0.084 mg/kg IM) given 30 min before nerve agent (SC). One minute after nerve agent, antidote given IM together with 14 mg/kg atropine; diazepam (1.8 mg/kg) given IM immediately after atropine plus antidote mixture.

ChE to bind nerve agent before it can reach tissue AChE sites (38) and the use of monoclonal antibodies (9,39) or carboxylesterase (40) and other nerve agent-inactivating enzymes (41) as protective systems. Again, while these approaches have likely value in military applications, they are in the research stage and are not at all likely to be available for consideration of use during the CSDP.

Protection of Civilian Populations

Given the potentially catastrophic effects of an inadvertent release of nerve agent with off-site exposure of the surrounding population, the distribution of antidotes of autoinjectors and/or prophylactic doses of pyridostigmine were considered in the Final Programmatic Environmental Impact Statement (1). The severe and possibly life-threatening toxic effects of even a 2-mg dose of atropine and of pralidoxime (15) were acknowledged to be a realistic consequence of inappropriate self-administration. Children, elderly, and those with cardiovascular conditions are considered particularly sensitive groups. The resulting recommendation is that autoinjectors not be distributed to the public. A further consideration in making this decision is the possibility of substance abuse with atropine, a hallucinogen (Table 1).

Extended pretreatment of the general population with pyridostigmine also poses the problem of toxic side effects in the event of an inadvertent overdose (9) which might be exacerbated in very young, elderly, or otherwise sensitive members of the civilian population. These side effects may include decreased visual acuity/accommodation and gastrointestinal effects. The visual effects could easily lead to severe consequences for an unsuspecting individual attempting to drive or perform other vision-dependent hazardous tasks. Thus, in a civilian population, extended pretreatment (prophylaxis) is not feasible or desirable.

Vesicant Agent Therapy

The blister agents, mustard and Lewisite, are very toxic

but are not acutely lethal at the extremely low doses characteristic of nerve agent toxicity. Rather, they were designed as effective incapacitating agents. Mustard agent in its various formulations is an alkylating agent that combines irreversibly with the proteins and nucleic acids of the cells it contacts. The signs of mustard poisoning are reviewed in detail elsewhere (1) and summarized in Watson, Jones, and Griffin (42). Mustard exposure is insidious in that there is usually a latent period of several hours before the toxic reactions appear. The most sensitive end point is eye irritation; skin rashes or blisters occur at larger doses and all exposed mucus membranes are susceptible to irritation, e.g., the respiratory tract membranes in an inhalation exposure. Latent effects such as vision impairment, chronic bronchitis, and skin and lung cancers are known to be caused by the large mustard exposures possible in warfare or in weapons factories during World Wars I and II (42).

The acute and latent toxic effects of Lewisite are reviewed in detail elsewhere (1). Lewisite produces immediate severe pain upon skin and eye exposure; it kills cells on contact by poisoning essential cell enzyme systems rather than by alkylating reactions. It is also a systemic poison, damaging the liver, gall bladder, and bile ducts and even kidneys and urinary tract at higher doses. It is implicated as a carcinogen at sublethal doses that cause blistering and pain.

Sulfur Mustard

There is no specific antidote known for sulfur mustard poisoning (43-45). Mustard is highly reactive chemically and forms a chemical bond with many biological molecules. Once this bond is formed, the reaction is irreversible for all practical purposes. Attempts to remove the mustard residue from biological molecules have been unsuccessful, except with drastic chemical procedures that would be injurious to living tissue (45,46). Treatment of sulfur mustard poisoning in humans has focused on rapid decontamination followed by symptomatic therapy (47). Discussions in U.S. Army manuals of therapy for various chemical warfare agents correctly emphasize that instantaneous removal of mustard from body surfaces is the best form of treatment (48). The recommended way to accomplish this is by washing with dilute household bleach (0.5% HTH) or copious amounts of soap and water (49,50). A study of the potential use of household products to remove mustard from guinea pig skin (51) indicated that most such products (tissue paper, flour, talcum powder, washing abrasive, salad oil, etc.) were effective in reducing skin damage if applied within 4 min of contamination. Flour sprinkled on the contaminated skin, followed by removal of the flour with wet tissue paper is particularly effective for physical removal, but does not chemically neutralize sulfur mustard. Neutralization is most readily accomplished by use of a 0.5% HTH solution.

U.S. Army documents (11,48,50) that discuss these chemical warfare agents also provide information regarding decontamination and first aid in the case of battlefield exposures. Emphasis is placed upon immediate decontamination following exposure to the sulfur mustard agents H and HD. Copious flushing with water for eye contamination and

bathing with dilute bleach solutions to remove skin contamination is recommended. Fuller's earth powder (which is used to adsorb liquid agent droplets) and chloramine powder (which reacts chemically with mustard) are effective skin decontaminants and have been supplied to military personnel in field kits in the past (45,52). The chloramine reaction alters mustard's chemical structure so that it no longer reacts with biological molecules. The chloramines, along with effective equipment decontaminants such as hypochlorite, operate by producing free chlorine, which chemically reacts with mustard (45,52). Such chemicals could be useful in reducing skin damage in accidentally exposed populations (if applied quickly enough after exposure). However, these chemicals can neither be used in the eye nor to alleviate respiratory tract damage. The current M258A1 skin decontamination kit will shortly be supplanted by a resin-based M291 skin kit that is easier to use (11).

Treatment and decontamination procedures described above for mustard agent are effective for HT exposure as well. Because HT is considered to be more toxic than HD, swift removal of the agent and treatment of symptoms are imperative. Personnel decontamination can be accomplished by washing with copious quantities of either water (HT is poorly soluble in aqueous solutions) or soap and water. Chlorine bleach solutions will neutralize HT, as will the reagents contained in the Army M258A1 and M291 skin decontamination kits.

Some animal studies have focused on use of drugs that might react with mustard as a mustard scavenger (47). Rat studies have indicated that in animals dosed with three times the LD₅₀ dose of mustard and injected with various drugs 30 min later, the best protective effects (decreased lethality, fewer pathological organ changes, less loss of body weight) were obtained with a combination of sodium thiosulfate, vitamin E, and dexamethasone (47). The dosages of drugs used were 3000 mg/kg of sodium thiosulfate, 8 mg/kg of dexamethasone, and 20 mg/kg of vitamin E. The sodium thiosulfate was thought to act as a mustard scavenger (i.e., simply reacted with mustard); vitamin E is considered an antioxidant and free-radical scavenger. Dexamethasone is a corticosteroid, an anti-inflammatory agent. Among rabbits receiving a dermal dose of mustard, use of steroid (cortisone) injections 15 min after treatment, or cortisone injections plus hydrocortisone ointment at the site of mustard application, reduced skin swelling and decreased the thickness of the skin lesion produced by mustard (53). This therapy did not hasten the rate of healing, however. These results with laboratory animals suggest that symptomatic therapy could have beneficial effects in human cases of mustard poisoning and that mustard scavengers may also be useful, but that such treatment must be initiated relatively quickly after exposure. It is to be emphasized that the previously described treatments are, to our knowledge, untested for their efficacy in humans.

Internal exposures do not lend themselves to decontamination and have no specific treatment. Depending on the dose, inhalation of mustard vapors will generate inflammation or ulceration of the respiratory tract and lungs. In exceptionally severe cases (50–70 mg/m³), death can result

from extensive tissue damage and fluid concentration in the lungs and trachea. Ingestion of contaminated food or water would produce nausea, gastrointestinal disturbances and diarrhea. Symptomatic and supportive therapy are recommended.

Lewisite

Historically, the antidote of choice for treating Lewisite and arsenical poisoning in general is the synthetic dithiol, 2,3-dimercapto-1-propanol, developed by British toxicologists in the years immediately prior to World War II (54). Known as British anti-Lewisite (BAL), this compound prevents skin vesication from Lewisite exposure after an untreated time lapse of as much as 1 hr. Intramuscular administration of BAL will also provide protection from topical and systemic Lewisite effects by binding arsenic to the BAL molecule, thus permitting transport of the arsenic complex to the excretory system and removal through the urine. Nevertheless, therapeutic administration must be closely monitored because BAL possesses considerable toxic properties of its own and will interfere with cellular respiration (54). BAL is suitable for muscular injection only. Recommended treatment and precautions are summarized in Table 6 (4,17). Following World War II, BAL use was expanded to include civilian medicine, where it has been an effective treatment in cases of lead, mercury, copper, and arsenic poisoning (55).

In the late 1950s, scientists in the Soviet Union and the People's Republic of China reported success with new, water-soluble BAL analogues in treating victims of occupational heavy-metal poisoning and in preventive therapy among workers in heavy metals industries (56–59). These new BAL analogues are the sodium salts of 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-dimercaptosuccinic acid (DMSA). In addition to being water soluble and exhibiting less toxicity than BAL, they possess the advantage of oral administration (not a recommended route for BAL treatment). Recent work in the U.S. demonstrates that both DMPS and DMSA protect rabbits receiving oral or subcutaneous (SC) doses of Lewisite from lethal systemic effects (59). Even when treatment was delayed for 90 min after Lewisite exposure, all exposed animals survived; in contrast, between 83 and 100% of the Lewisite-exposed animals receiving no treatment died (59).

Preliminary experiments on the skin of swine indicate that pretreatment with DMPS or DMSA in a thin collagen film may also be protective against the blistering action of Lewisite on the skin (59). This technique would have utility for emergency workers and rescue teams who may need to enter contaminated areas or handle/treat contaminated individuals. Further studies on swine skin have demonstrated the effectiveness of another compound developed in the Soviet Union [Mercaptid; 3-(*p*-tolylthio)-1,2-propanethiol] in dealing with postexposure treatment of Lewisite-contaminated skin; topical application of Mercaptid "diminished the severity of the burns" as observed in a nonquantitative visual assay of exposed swine skin (59). Note that swine skin is considered by many investigators to be reasonably similar

Table 6. Treatment protocol for British anti-Lewisite (BAL) (2,3-dimercapto-1-propanol) (dimercaprol).

Antidote/action	Dose	Overdose symptoms, management
Lifesaving in acute poisoning of arsenicals (except arsine) and solutions of organic Hg compounds. Also for chronic As or Au poisoning.	IM into buttocks in dosage of 0.5 mL/25 lb body weight (commercial preparation of 10% BAL in peanut oil) up to maximum of 4.0 mL. Repeat in 4, 8, 12 hr. For severe cases, interval shortened to 2 hr. ^a	Symptoms Consistent objective response is rise in systolic and diastolic blood pressure plus tachycardia (rapid heartbeat). Nausea and sometimes vomiting Headache Burning sensation of lips, mouth Feeling of constriction in throat, chest, hands Conjunctivitis, tearing, salivation Hand tingling Burning sensation in penis Sweating forehead and hands Abdominal pain Tremors Lower back pain Anxiety, weakness, and restlessness Tachycardia (rapid heartbeat) and elevated arterial blood pressure Persistent fever in children Occasional painful sterile abscesses at injection sites Coma and convulsions at high dose (in children, this occurs at 10, 25, and 40.5 mg/kg) (recovery prompt) ^b
Action by displacing the metal from its combination with sulfhydryl groups of enzyme proteins. ^b		
Toxicity rating 4, very toxic (Probable oral lethal dose = 50-500 mg/kg or 1 teaspoon to 1 ounce for 150-lb [70-kg] person.) ^b		Management Symptoms usually subside in 30-90 min; IM use of 1:100 solution epinephrine HCl (0.1 to 0.5 mL) or oral ephedrine sulfate (25-50 mg) ^b

^aFrom Sidell (4).

^bFrom Gosselin et al. (17).

to human skin in its reaction to certain surface-active chemicals.

Dosage and treatment protocols for use of DMPS and DMSA in Lewisite poisoning have not yet been developed because these compounds are considered "orphan drugs." However, DMPS and DMSA have been used to treat several isolated cases of arsenic and methylmercury poisoning (60,61) and to reduce the body burden of lead among smelter workers (62). Treatment for one arsenic-poisoned individual was 300 mg DMSA orally every 6 hr for three days; the victim recovered. However, prolonged oral treatment (>5 days) with some formulations of DMPS has been associated with development of Stevens-Johnson syndrome (J. J. Chisholm, personal communication).

An additional Lewisite antidote that has not seen much use since the end of World War II is 2,3-dimercaptopropanol glucoside (BAL-INTRAV), another BAL formulation developed for IV and SC treatment of topical Lewisite exposure and systemic effects (63). BAL-INTRAV also demonstrates a lower mammalian toxicity than BAL (LD₅₀ in rabbits for BAL-INTRAV is 5000 mg/kg as compared to 50 mg/kg for BAL) (63). A further advantage of BAL-INTRAV therapy is the relatively lengthy time delay that can occur between exposure and treatment with no observed change in successful outcome, at least for laboratory rabbits. With a delay of 4 hr, treated rabbits exhibited lesions at the site of Lewisite application, "but made an uneventful recovery" (63). A delay of 6.5 hr permitted eventual full recovery after 1 to 3 days of poor appetite and illness. A delay of 12 hr was fatal to all exposed rabbits (63). The above values were observed in test populations of adult rabbits; younger animals (with thinner skins) were more sensitive to Lewisite

exposure. At the same dose as the adults (1.5 mg/kg), none of the young rabbits survived a 6.5-hr delay in treatment with BAL-INTRAV; all survived a 4.0-hr delay.

Although wartime conditions prevented larger populations of experimental animals from being tested, the investigations performed by Danielli and his colleagues (63) demonstrate that BAL-INTRAV has merit in Lewisite therapy, that time before treatment should be kept at a minimum, and that young individuals should be treated sooner after Lewisite contamination than adults.

In the absence of BAL analogues for treating exposed skin, decontamination may be accomplished by washing with water, soap and water, or solutions of chlorine bleach (0.5% HTH) or soda (sodium hydroxide), and use of absorbent powders such as Fuller's earth (49,50,52). As previously discussed, exposed eyes should be immediately flushed with large amounts of water or weak solutions of soda or detergent.

Conclusions

Antidotes or combinations of antidotes are available to counteract the effects of exposure to GA, GB, and VX. In adequate dosage, the antidotes must be used in conjunction with prompt decontamination, intensive monitoring, and individualized supportive therapy, especially in cases of severe exposure. Incapacitation and respiratory failure can occur even with prompt antidote administration. The latter effects can recur after apparent improvement, so continuous monitoring and repeated administration of antidotes and artificial respiration may be required, especially in the first 24 hr after exposure. Neither distribution of atropine

and oxime autoinjectors to the general public nor precautionary administration of protective drugs to the general population are recommended.

Since there are no known antidotes for sulfur mustard poisoning, prompt decontamination becomes of highest importance. One approved antidote, BAL, exists for Lewisite. Other promising analogues exist that have superior properties, but they are not generally available.

Management of decontamination and immediate treatment for multiple casualties, particularly in cases of moderate to severe exposure to nerve agents is complex, and the details of management of nerve agent as opposed to organophosphate pesticide poisoning differ. These facts lead to the recommendation that medical and emergency aid personnel (first responders) in the vicinities of chemical weapons stockpile sites receive training in management of medical emergencies involving nerve and blister agents prior to the onset of the CSDP. While on-site training tailored for first responders is offered by the Atlanta-based Centers for Disease Control (2), training geared for physicians is available from the Chemical Casualty Care Office of the U.S. Army Medical Research Institute of Chemical Defense at Aberdeen Proving Ground, Maryland. We recommend that host communities avail themselves of these resources.

The potential for simultaneous exposure of a substantial number of humans and the consequent need for significant amounts of antidotes may require local stockpiling of antidotes. Pralidoxime may be problematic since it is available from only one supplier (Wyeth-Ayerst Laboratories, New York, NY). Inventories of existing local supplies of antidotes and decontamination kits should be made and a depot system set up in advance of the active phase of the CSDP if projected needs warrant it.

In summary, a low but credible probability exists for a catastrophic accidental release (>1000 fatalities) of warfare agents during storage or in the course of the CSDP. Neither antidote autoinjector distribution to the general population nor extended prophylactic pretreatment of the population with pyridostigmine are acceptable options. Existing medical resources would be severely strained to deal with hundreds or thousands of casualties requiring decontamination and treatment. Consequently, every effort must be made to have trained personnel, decontaminants, and antidotes at hand in advance to provide immediate care and necessary long-term treatment.

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