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PREVENTION AND TREATMENT OF INJURY FROM CHEMICAL WARFARE AGENTS

The recent terrorist attacks on the US have led to many questions about the clinical effects, prevention and treatment of injury caused by chemical warfare agents.

NERVE AGENTS

Like organophosphate insecticides, nerve agents phosphorylate and inactivate acetylcholinesterase, leading to accumulation of acetylcholine at nicotinic and muscarinic receptors, and at other receptors in the central nervous system (CNS). Nerve agents that have been used in chemical weapons include tabun (GA), sarin (GB), soman (GD), cyclosarin (GF) and VX. At room temperature, all except VX are volatile. VX has the consistency of motor oil and becomes volatile only at high ambient temperatures. Nerve agent vapors are denser than air and tend to accumulate in low-lying areas. All nerve agents are lipophilic and hydrophilic, rapidly penetrating clothing, skin and mucous membranes.

CLINICAL EFFECTS – Exposure to a liquid or vapor nerve agent produces dose-dependent peripheral and CNS effects ([T Suzuki et al, Lancet 1995; 345:980](#)). Respiratory effects include rhinorrhea, bronchorrhea and bronchospasm (muscarinic), respiratory muscle paralysis (nicotinic) and depression of CNS respiratory drive. Cardiovascular effects include bradycardia and heart block (muscarinic) or tachycardia (nicotinic). CNS effects range from headache, agitation and vertigo to rapidly decreasing level of consciousness and seizures. Peripheral motor effects include initial fasciculations followed by flaccid paralysis (nicotinic). Gastrointestinal effects include nausea, vomiting and diarrhea (muscarinic). Ocular effects include miosis, eye pain, blurred vision, dim vision, conjunctival injection and tearing (muscarinic) ([T Okumura et al, Ann Emerg Med 1996; 28:129](#)).

Liquid – Dermal exposure to a large dose of liquid nerve agent may be transiently asymptomatic (10-30 minutes), followed by rapid onset of respiratory and neurologic effects. With dermal exposure to a minimal amount of nerve agent liquid, the onset of localized symptoms (sweating, fasciculations) may be delayed for up to 18 hours.

Vapor – Inhalation of a large amount of nerve agent vapor causes fulminant respiratory failure within seconds to minutes. Exposure to a small amount of vapor typically produces more limited ocular (miosis, eye pain) and airway (hypersecretion, bronchospasm) effects.

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GAS MASKS — Use of military gas masks by untrained civilians is not recommended; the usual full-face mask imposes a large respiratory load and excessive dead space. The ability of military gas masks (e.g., a US military M40 mask) to provide ocular and respiratory protection depends on the fit and the integrity of the filter canister, which can be damaged by handling, water and excessive breathing pressures and must be replaced every 30 days. In Israel during the Gulf War, improper use of gas masks by civilians resulted in 13 deaths due to suffocation (failure to remove the filter cap creates a negative-pressure suction effect that can make the masks difficult to take off), and a total of 114 people died from cardiorespiratory causes while using masks in sealed rooms ([P Barach et al, Ann Emerg Med 1998; 32:224](#)).

PRETREATMENT WITH PYRIDOSTIGMINE — Pyridostigmine bromide (*Mestinon*) is an acetylcholinesterase inhibitor with a short half-life used in the treatment of myasthenia gravis; by binding to peripheral acetylcholinesterase for several hours, it temporarily blocks inactivation by nerve agents. Pyridostigmine itself does not counteract the effects of the nerve agents; it only enhances the effects of antidotes. The usual adult dose is 30 mg PO q8h ([FR Sidell and J Borak, Ann Emerg Med 1992; 21:865](#)). If there is a risk of imminent exposure, one dose of pyridostigmine at least 2 hours before may be helpful; 2 doses 8 hours apart are preferable. In animal studies, pretreatment with pyridostigmine has been effective against tabun or soman, ineffective against sarin or VX, and variably effective against cyclosarin, depending on the species.

DECONTAMINATION — Patients exposed to liquid nerve agent require immediate decontamination to prevent further absorption. Decontamination consists of rapid removal of clothing and jewelry, followed immediately by irrigation with tepid water and washing with soap and water. If water is limited or unavailable, 0.5% hypochlorite solution, which inactivates nerve agents, can be helpful ([AG Macintyre et al, JAMA 2000; 283:242](#)).

ANTIDOTES — Even in severe cases of nerve gas exposure, treatment with antidotes can be life-saving ([H Nozaki et al, Lancet 1995; 345:980](#)).

Atropine — Atropine is a competitive inhibitor of acetylcholine at muscarinic receptors that reverses the hypersecretory, bronchoconstrictive and gastrointestinal effects of nerve agents. The usual adult dose of atropine is 2 mg IM for mild dyspnea and 6 mg for severe dyspnea. Appropriate therapeutic end points are drying of secretions and ease of ventilation. Heart rate and pupil size are poor clinical indicators of adequate atropinization, since tachycardia may reflect hypoxemia, stress or severe nicotinic effects, and miosis may persist for weeks. Repeat 2-mg doses can be given every 5-10 minutes; patients with nerve agent exposure rarely require more than 20 mg of atropine in the first 24 hours.

Pralidoxime Chloride — Pralidoxime chloride (*Protopam Chloride*) is an oxime acetylcholinesterase reactivator that binds to the nerve agent, removing it from its binding site and reversing muscle weakness. It should be given at the same time as atropine. Early administration is critical, since pralidoxime is only effective when administered before the nerve agent-acetylcholinesterase bond becomes permanent ("ages"); the time it takes for half of the nerve agent to "age" is about 2 minutes for soman, 5 hours for sarin, 13 hours for tabun, and 48 hours for VX. The usual dose of pralidoxime is 1-2 g IV or IM. IV doses should be given over 20-30 minutes to prevent hypertension. Pralidoxime can be repeated at hourly intervals, if necessary, or continuously at 500 mg/hour by IV infusion.

Diazepam — Early administration of the anticonvulsant diazepam (*Valium*, and others) 10 mg IM may prevent permanent CNS damage in patients with severe nerve agent toxicity.

Tropicamide – Tropicamide (*Mydracyl*), a topical cycloplegic-mydriatic agent, blocks cholinergic stimulation of the iris sphincter muscle and ciliary body, relieving nerve-agent-induced eye pain (T Kato and T Hamanaka, *Am J Ophthalmol* 1996; 121:209). The adult dose is 1-2 drops of 0.5% solution in each eye, repeated as needed.

Auto-Injectors – Spring-loaded auto-injectors for intramuscular use containing (separately) atropine 2 mg, pralidoxime 600 mg, diazepam 10 mg and morphine 10 mg are available, currently to government agencies only, from Meridian Medical Technologies, Columbia, MD (www.meridianmeds.com/civdef.html).

CONCLUSION – Nerve agents inactivate acetylcholinesterase, causing cholinergic excess that leads to life-threatening respiratory and neurologic compromise. Treatment with atropine and pralidoxime can be life-saving.

VESICANTS

Sulfur mustard, an oily liquid that vaporizes at high ambient temperatures, is the most common vesicant used in chemical weapons. Mustard is lipophilic and readily penetrates skin, most textiles and rubber. It irreversibly alkylates DNA, RNA and protein, causing cell death. Moist, warm tissues (mucosa, perineum, axillae) are most vulnerable, because the chemical reaction is water- and temperature-dependent.

CLINICAL EFFECTS – Dermal exposure to liquid mustards causes burns that progress from superficial (erythema, pain) to partial thickness (bullae) and, uncommonly, to full thickness (deep bullae, ulcers). Skin contact with sulfur mustards may produce pain after a delay of minutes to hours. Inhalation exposure to mustard vapor can cause mucosal sloughing and airway obstruction. Ocular effects from exposure to liquid or vapor mustard range from ocular irritation and conjunctivitis to corneal burns and blindness. After exposure to high doses, bone marrow suppression can begin in 3-5 days, resulting in leukopenia that reaches its nadir around day 10, followed by thrombocytopenia and sometimes anemia. Nausea and vomiting are common 4-5 days post-exposure; diarrhea and bleeding can occur (J Borak and FR Sidell, *Ann Emerg Med* 1992; 21:303).

TREATMENT – Patients exposed to sulfur mustard require rapid removal of clothing, followed immediately by flushing with soap and water (KG Davis, *Ann Emerg Med* 2001; 37:653). Sloughing of the airway epithelium requires endotracheal intubation. Overhydration should be avoided; chemical burns produce less fluid loss than thermal burns. Mustard burns are especially painful and require liberal opioid analgesia. Severe burns usually require irrigation, debridement and topical antibiotics such as silver sulfadiazine 1% (KJ Smith, *Dermatol Clin* 1999; 17:41). Eye care includes irrigation, topical antibiotics and cycloplegic-mydriatics; application of petroleum jelly can prevent burned lids from sticking (MR Safarinejad et al, *Mil- it Med* 2001; 166:67). Granulocyte colony-stimulating factor or filgrastim (*Neupogen* – Medical Letter 1991; 33:61) can be used for treatment of mustard-induced neutropenia (JJ Costa, *J Allergy Clin Immunol* 1998; 101:1).

CONCLUSION – Mustard reacts with the skin, eyes and respiratory tract to cause chemical burns and with the bone marrow to cause pancytopenia. Rapid decontamination and treatment with appropriate drugs can be helpful.

PULMONARY TOXICANTS

The pulmonary toxicants most likely to be used as chemical weapons include chlorine, phosgene and diphosgene, which all exist as gases under ambient conditions. Diphosgene readily degrades to phosgene and nontoxic levels of chloroform. Pulmonary toxicants are denser than air and accumulate in low-lying areas. Chlorine, phosgene, and diphosgene all react with water to produce hydrochloric acid, which damages tissue, but phosgene also acylates amino, hydroxyl and sulfhydryl groups in tissue, causing a chain of oxidative injury. The most common sites of injury are mucous membranes such as the conjunctiva and respiratory tract, including the alveolar-capillary membrane.

CLINICAL EFFECTS — Chlorine dissolves readily in the moist mucosa of the upper respiratory tract, producing rhinorrhea, hypersalivation and laryngeal edema, as well as lower respiratory tract reactions such as coughing, wheezing and rales (C Winder, *Environ Res* 2001; 85:105). Phosgene and diphosgene, which are relatively insoluble, pass further into the respiratory tract where they are more slowly absorbed, producing bronchoalveolar injury, dyspnea, bronchospasm and permeability pulmonary edema. Clinical effects of pulmonary toxicants vary with the concentration and duration of exposure. Low-dose inhalation causes minor pulmonary irritation and bronchospasm. High-dose inhalation may produce laryngospasm, pneumonitis and acute lung injury with acute respiratory distress syndrome (ARDS). The delayed onset of ARDS (up to 48 hours in initially asymptomatic patients) is characteristic of pulmonary toxicant inhalation.

TREATMENT — Oxygen — Supplemental oxygen may improve tissue oxygenation in patients with pulmonary signs and symptoms. Airway or ventilatory compromise requires intubation. Ventilatory support management of ARDS requires positive end-expiratory pressure.

Bronchodilators — Beta₂-adrenergic agonists relax airway smooth muscle, increasing airway diameter and reducing hyperactivity in pulmonary toxicant inhalation (JD Sexton and DJ Pronchik, *J Toxicol Clin Toxicol* 1998; 36:87). The usual adult dose of albuterol (*Proventil*, and others) is 2.5 mg in 3 ml of sterile water, nebulized and repeated as needed. Theophylline may also be helpful (AM Sciuto et al, *Exp Lung Res* 1997; 23:317).

Corticosteroids — Corticosteroids such as prednisolone have been used in an attempt to prevent pulmonary edema in the asymptomatic latency phase following phosgene inhalation. The dose of prednisolone has been 250 mg IV. A dose of 1 g IV has been recommended for treatment of phosgene-induced pulmonary edema (J Borak and WF Diller, *J Occup Environ Med* 2001; 43:110). Whether it would also be helpful for chlorine inhalation is unknown.

Others — In animals, one or two large doses of ibuprofen decreased the toxicity of exposure to phosgene (AM Sciuto et al, *J Appl Toxicol* 1996; 16:381). An acetylcysteine aerosol, 20 ml of a 20% solution given by nebulizer, has also been effective in animals.

CONCLUSION — Pulmonary toxicants cause inhalation injury ranging from mucosal irritation and bronchospasm to ARDS. Treatment with appropriate drugs can be life-saving.

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