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DEPARTMENT OF THE ARMY TECHNICAL BULLETIN

ANTICHOLINESTERASE INTOXICATION: PATHOPHYSIOLOGY, SIGNS AND SYMPTOMS, AND MANAGEMENT

Headquarters, Department of the Army, Washington, D.C.
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1. Introduction. *a.* Anticholinesterase compounds are among the most toxic chemical substances known. Most are esters of phosphoric acid, such as the highly toxic nerve agents (tabun (GA), sarin (GB), soman (GD) and VX) and many common insecticides (Parathion, Malathion, Systox), but some belong to the group of carbamate compounds (physostigmine or prostigmine). All produce physiological effects by inhibiting the cholinesterase enzymes distributed throughout the nervous system.

b. Nerve agents can be dispersed by artillery shell, mortar shell, rocket, aircraft spray, and land mine. Pesticide exposures are commonly due to carelessness among cropdusters, to attempts at suicide, or to careless use of these materials by the home gardener. Absorption may occur via the skin or the respiratory and gastrointestinal tracts with resulting variations in the sequence of observed effects.

2. Purpose. The purpose of this bulletin is twofold:

a. To describe the signs and symptoms of anticholinesterase poisoning for diagnostic purposes.

b. To describe the treatment of anticholinesterase poisoning.

3. Properties. The nerve agents are colorless to light brown liquids. Some, those of the G series, are quite volatile and evaporate rapidly from contaminated areas; others (such as VX) are relatively stable liquids at ordinary temperatures and may persist on terrain and foliage for days or weeks. Except for GA, which has a faint fruity odor, they are odorless and even in highly toxic aqueous concentrations are tasteless. Most organophosphate compounds react slowly with water and rapidly with alkali solutions yielding hydrolysis products which are non-toxic or con-

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siderably less toxic than the compounds themselves.

4. Pathophysiology: Signs and Symptoms.

a. In general the peripheral nervous system of the human body makes use of either of two chemical neurotransmitters. The neurons of the sympathetic nervous system release norepinephrine to carry the final impulse to the end organs. Those of the parasympathetic system release acetycholine. Acetylcholine also plays a vital role in the innervation of skeletal muscle, autonomic ganglia, and many structures within the central nervous system. If the end organ is muscle, either skeletal or smooth, it contracts; if it is a gland, it secretes; and if it is another nerve cell, its probability of firing is altered.

b. The duration of action of acetylcholine is limited by diffusion and by the rapid hydrolytic action of acetycholinesterase, which is located near receptor sites in the end organ. Cholinesterase inhibitors permit acetylcholine to persist at these sites, mimicking the effects of a massive release of acetylcholine. The major effects are (1) those on skeletal muscle, e.g., initial stimulation with uncoordinated contractions, followed by fatigue and eventual flaccid paralysis; (2) those on the sites innervated by the parasympathetic nervous system, e.g., miosis, rhinorrhea, bronchoconstriction, increased gastrointestinal motility with nausea, vomiting, and diarrhea, secretion of the glands of the mouth, bronchi and gastrointestinal system, and bradycardia; and (3) those on the central nervous system, e.g., disturbances in thought, convulsions, coma and lethal depression of the vital centers of the brain. A complete list of signs and symptoms is given in table I.

c. The exact sequence and severity of the signs and symptoms depend on the route and total dose as well as the acuteness of exposure. If moderate exposure to vapor or aerosol occurs, unprotected individuals may rapidly develop miosis (with impaired night vision and conjunctival injection), rhinorrhea, and tightness in the chest (due to bronchoconstriction and bronchorrhea). If the exposure is minimal, only one or two of these signs and symptoms may appear. If the exposure is heavy, these local effects will soon be followed by systemic signs and symptoms as the compound reaches the circulation after absorption from the respiratory tract, the skin, and the eyes. Thus intermingled in sequence would appear nausea, vomiting, perhaps diarrhea, mild to severe mental signs and symptoms (such as confused speech or convulsions), muscular fasciculations progressing to paralysis, anoxia, convulsions, and respiratory arrest due to depression of the centers of respiration in the brain. Death usually results from anoxia due to the combination of bronchoconstriction, bronchorrhea, respiratory muscle paralysis, and central respiratory depression.

d. Should the exposure be percutaneous, with droplets or powder, the sequence of signs and symptoms will be different. Local muscular twitching and sweating at the site of exposure may be the first signs, followed by the systemic effects described above. Because of slow passage through the skin, death may not occur for one or more hours following such exposures, except when the dose is relatively massive.

e. Exposure by the gastrointestinal route produces an initial symptom complex similar to that seen after percutaneous exposure except that the local percutaneous effects are absent. Nausea, vomiting, and diarrhea are followed by fatigue, weakness, perhaps mental signs, convulsions, and paralysis leading to death. The time course may be minutes to hours depending on the dose.

f. It is important to remember that following exposure by the percutaneous or gastrointestinal route (ingestion) the miosis, rhinorrhea and bronchoconstriction so characteristic of anticholinesterase poisoning by the vapor route may occur only very late or may not occur at all.

5. Therapy. The four cardinal principles of therapy for nerve agent intoxication are: assisted ventilation; cholinergic blockade (atropine); decontamination; and enzyme reactivation with pralidoxime chloride.

a. Assisted Ventilation. In the case of the severely intoxicated individual with marked bronchoconstriction, copious secretions in the tracheobronchial passages, paralysis of the respiratory muscles, central respiratory depression, hypoxia, convulsions, and death quickly ensue unless assisted ventilation is carried out. In an uncontaminated atmosphere this may be done by the standard

mouth-to-mouth method after rapid decontamination of the casualty's face and mouth. In a contaminated atmosphere the use of the M17A1 field protective mask and resuscitation tube is essential. In a well equipped medical facility, mechanical resuscitators of the positive pressure demand type may be used in conjunction with endotracheal intubation or tracheotomy.

b. Cholinergic Blockade (Atropine).

(1) As an anticholinergic drug, atropine acts by inhibiting the muscarinic parasympathetic effects of acetylcholine (e.g.; excessive secretions and smooth muscle spasm), but has no effect on the skeletal neuromuscular blockade.

(2) Emergency field therapy involves the use of the atropine automatic self-injection device which is a hard plastic tube containing 2 mg of atropine in solution (0.7 ml) and an injection needle which is triggered by a coiled spring mechanism. Each soldier carries three automatic injectors in his protective mask carrier and is instructed to self inject in the antero lateral (outside front) aspect of the thigh at the level to which the hand falls naturally. One automatic injector should be used at onset of symptoms and a second or third at 5 to 10 minute intervals if no improvement occurs.

(3) The emergency field therapy permits *anyone* to administer up to 6 mg of atropine to control symptoms. However, total dosage of atropine beyond 6 mg is administered by or under the control of a Medical Officer. The continued administration of atropine is maintained on schedule, as listed below, until signs of atropinization (dry mouth and skin) are achieved.

(4) If MILD symptons are presented by the casualty, 2 mg of atropine is injected intramuscularly at 20-minute intervals until atropinization occurs. If MODERATE symptoms are noted, then 2 mg of atropine at 10-minute intervals is administered. A mild atropinization then should be maintained for at least 24 hours by the intramuscular or oral administration of 1 or 2 mg of atropine at intervals of 1/2 to 4 hours.

(5) If SEVERE symptoms are noted, then 4 to 6 mg of atropine should be injected intravenously, or, if this is not feasible, intramuscularly. If the muscarine-like symptoms are not relieved and signs of atropinization do not appear, the intravenous injection of atropine in doses of 2 mg should be repeated at 3-to-8-minute intervals until this occurs. A mild degree of atropinization should then be maintained for at least 48 hours. In severe nerve agent poisoning the apparent effect of each injection of atropine may be transient, lasting only 10 to 30 minutes. In such cases the casualty must be observed continuously and atropine repeated as often as necessary to relieve the peripheral muscarine-like and central nervous system effects of the nerve agent. A total of 50 mg of atropine or even more may be given in the first 24 hours.

c. Decontamination.

(1) In a contaminated atmosphere one must think of self protection first, and this involves donning a protective mask and protective clothing, including gloves and boots if available.

(2) The casualty must be removed from the toxic environment and his clothing immediately removed, especially if the agent is a nonvolatile one such as VX, as it may continue to be absorbed through the clothing.

(3) The casualty should be washed liberally with water by any means available. The use of a bleaching agent such as sodium hypochlorite may help to detoxify the agent prior to the use of water. If ingestion of nerve agent is known to have occurred, gastric lavage with water should be carrier out.

d. Enzyme Reactivation, Pralidoxime Chloride (2-PAM C1).

(1) Pralidoxime chloride (2-PAM C1) is an oxime which increases the effectiveness of drug therapy in poisoning by some, but not all, cholinesterase inhibitors. Unlike atropine, it acts by reactivating the inhibited enzyme at nicotinic as well as muscarinic sites and therefore relieves the skeletal neuromuscular block.

(2) The dosage schedule of 2-PAM C1 depends on the degree of intoxication. In very SEVERE cases, 2 grams in 10 ml of sterile water should be given slowly intravenously (500 mg/min). Alternatively, 1 or 2 grams may be diluted in 150 ml of normal saline (or 5 percent dextrose and water) and administered intravenously over 15 to 30 minutes. This may be repeated after 1 or 2

hours if necessary. In MODERATE nerve agent intoxication, probably 1 gram intravenously will suffice. If intravenous administration is not feasible, intramuscular injections should be given. In MILD intoxication, 4 or 6 grams of 2-PAM C1 may be given orally, but the oral route is not generally recommended. Repeated doses are not usually required unless continued absorption (as from a skin depot) or metabolic change (as the metabolism of parathion to paroxon) is a probability.

(3) Common side effects of 2-PAM C1 are dizziness, headache, blurred vision, nausea, and impaired accommodation. Marked hypertension may occur during intravenous infusion and thus blood pressure should be monitored accordingly, but hypertension is usually transient. It should be noted that 2-PAM C1 may act as a weak anticholinesterase itself and thus unnecessary overdosage should be avoided.

e. Supportive Care.

(1) A patient intoxicated with an anticholinesterase compound presents a medical emergency of the most critical type and requires immediate intensive medical and nursing care, perhaps for days or weeks.

(2) The acute phase of the emergency is the immediate period of anoxia and depression of respiration. Assisted ventilation may be necessary for many hours. Repeated doses of atropine may be required to keep the patient in the state of mild atropinization; doses of 50 to 100 mg over the first 24 hours are not uncommon. To care for one cyanotic, anoxic, convulsing casualty who is suffering from anticholinesterase intoxication requires the full time of at least one medical officer and one or two aidmen or nurses. Even when respiration is finally restored to normal, the patient may remain unconscious and comatose for hours or days. This may be a direct central depressive effect of the poison and hence reversible or, more likely, particularly if the patient has been unconscious for over a day, this may be a consequence of prolonged anoxia causing a permanent brain damage.

(3) General supportive care, such as intravenous feeding, restoring electrolyte balance, treatment of shock, appropriate therapy for infection should it occur, etc., is no different from that necessary under other circumstances.

6. Laboratory diagnosis. *a.* Two types of circulating cholinesterase (ChE) can be measured by routine laboratory techniques: (1) red blood cell (acetyl, "true") ChE, and (2) plasma (butyryl, "pseudo") ChE. Although the functions of these cholinesterases in the red cell and in the plasma are unknown, they reflect in a very general way the concurrent level of tissue cholinesterase. Whole blood ChE (a mixture of red blood cell and plasma ChE) determinations are rather simple procedures and are satisfactory in emergency situations.

b. A 10-ml sample of blood should be collected for ChE analysis in a heparinized vacutainer or withdrawn by syringe and placed in a test tube containing 0.2 ml of heparin (1,000 units/ml), and mixed gently. These tubes should be packed in ice (*not dry ice*) for shipment to the laboratory. Three methods for measuring ChE in the samples are described in the following reports:

Michel, H. O. An Electrometric Method for the Determination of Red Blood Cell and Plasma Cholinesterase Activity. J. Lab. Clin. Med. *34,* 1564-1568 (1949).

Groff, W. A., Mounter, L. A., and Sim, V. M. A Multi-Channel Analytical System for Continuous Monitoring of Blood Cholinesterase. In Technicon Symposium on Automation in Analytical Chemistry. New York, N. Y. October 1966.

Fleisher, J. H., Woodson, G. S., and Simet, L. A Visual Method for Estimating Blood Cholinesterase Activity. Arch. Indus. Health *14,* 510-520 (1956).

c. Red cell ChE may be depressed in certain anemias (pernicious anemia, paroxysmal nocturnal hemoglobinuria) or, very rarely, depression may be congenital in origin. The plasma ChE may be depressed because of certain disease states, particularly hepatocellular disease, and when depressed because of congenital factors is associated with a heightened susceptibility to succinylcholine and similar drugs. Circulating ChE also may be quite severely depressed without clinical signs or symptoms in an individual who has sustained repeated small exposures to an anticholinesterase compound over several days or over a much longer period. Such a

circumstance can be difficult to diagnose.

d. Different types of anticholinesterases preferentially depress either red cell or plasma cholinesterase. Mild nerve agent poisoning will cause a depression of both the red cell and plasma ChE; many insecticides, particularly some of the carbamate type, often depress plasma ChE more severely than red cell ChE. In severe poisoning with any anticholinesterase both enzymes will be markedly depressed.

e. When an exposure to an anticholinesterase is by the vapor/aerosol route and the only signs and symptoms are those of the local type (miosis, rhinorrhea, or mild bronchoconstriction), the circulating ChE may or may not be depressed, depending on the amount of chemical absorbed.

f. When systemic symptoms are produced, whether the exposure is by the respiratory, percutaneous, or gastrointestinal route of absorption, the ChE will be depressed, usually quite severely (below 30 percent of the baseline, or "normal" value).

g. As a guide, in the absence of a disease or other causes, a ChE value of less than 50 percent of an individual's baseline value indicates an exposure to an anticholinesterase. Following an acute exposure systemic symptoms may be associated with a level below 30 percent of baseline.

h. The regeneration or return of ChE to normal varies with the anticholinesterase compound and therapy. Anticholinesterase compounds are usually classed as "reversible" or irreversible." "Reversible" compounds are those which do not produce a firm bond between the agent and the ChE. "Irreversible" compounds produce a firm bond between agent and enzyme. One of the factors involved in this is called "ageing," which in effect means the time required to produce bonding. For some compounds, GD for example, the half-life for ageing in human red cell ChE is around 5 minutes; for other compounds, VX for example, the half-life is several hours. Thus, time of administration of 2-PAMC1 is important if there is to be an effective reversal of inhibition of the enzyme. Not all compounds can be successfully treated with 2-PAMC1 regardless of whether it is given immediately after poisoning; GD is an example.

7. Sequelae. After recovery from a moderate or severe intoxication by an anticholinesterase, the patient may feel "subpar" for weeks or even months. He may feel tired, fatigue easily, have a poor appetite, and have continuing mental symptoms, such as impaired concentration, and may report dreams. These symptoms gradually resolve over a period of 2 to 3 months.

Table 1. Signs and Symptoms of Nerve Agent Poisoning

	Site of action	*Signs and symptoms*
		following local exposure
1.	Muscarine-like:	
	Pupils	Miosis, marked, usually maximal (pinpoint), sometimes unequal.
	Ciliary body	Frontal headache, eye pain on focusing, slight dimness of vision, occasional nausea and vomiting.
	Conjunctivae	Hyperemia.
	Nasal mucous membranes Bronchial tree.	Rhinorrhea, hyperemia. Tightness in chest, sometimes with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, cough.
		following systemic absorption
	Bronchial tree	Tightness in chest, with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, dyspnea, slight pain in chest, increased bronchial secretion, cough, pulmonary edema, cyanosis.
	Gastrointestinal	Anorexia, nausea, vomiting, abdominal cramps, epigastric and substernal tightness (cardiospasm) with "heartburn" and eructation, diarrhea, tenesmus, involuntary defecation.
	Sweat glands	Increased sweating.
	Salivary glands	Increased salivation.
	Lacrimal glands	Increased lacrimation.
	Heart	Slight bradycardia.
	Pupils	Slight miosis, occasionally unequal, later maximal miosis (pinpoint).
	Ciliary body	Blurring of vision.
	Bladder	Frequency, involuntary micturition.
2.	Nicotine-like:	
	Striated muscle	Easy fatigue, mild weakness, muscular twitching, fasciculations, cramps, generalized weakness, including muscles of respiration, with dyspnea and cyanosis.
	Sympathetic ganglia	Pallor, occasional elevation of blood pressure.
3.	Central Nervous System	Giddiness, tension, anxiety, jitteriness, restlessness, emotional lability, excessive dreaming, insomnia, nightmares, headaches, tremor, withdrawal and depression, bursts of slow waves of elevated voltage in EEG, especially on overventilation, drowsiness, difficulty concentrating, slowness on recall, confusion, slurred speech, ataxia, generalized weakness, coma, with absence of reflexes, Cheyne-Stokes respirations, convulsions, depression of respiratory and circulatory centers, with dyspnea cyanosis, and fall in blood pressure.

By Order of the Secretary of the Army:

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