ORGANOPHOSPHATE OVERDOSE

Sergei, Zacharrev, MD (2003-2004)

Organophosphate insecticides originated as compounds utilized initially as nerve gases in the early wars of the twentieth century and include warfare agents, organophosphorous compounds and carbamate insecticides, and medicinal agents. In the late 1990s and 2000, with the advent of increased awareness of terrorism, nerve agents have gained prominence as weapons of mass destruction.

Pharmacology

- Highly lipid soluble \(\rightarrow\) readily absorbed via dermal, GI, respiratory routes; deposition in body fat
- Some are metabolized to more potent acetylcholinesterase inhibitors and onset of clinical toxicity may be delayed.

Pathophysiology

- Competitive inhibition of acetylcholinesterase, this occurs both at tissue sites (true acetylcholinesterase or butyrylcholinesterase) and in plasma (circulating pseudocholinesterase) \(\rightarrow\)
- Results in accumulation and prolonged effect of acetylcholine at a variety of neurotransmitter receptors, including sympathetic and parasympathetic ganglionic nicotinic sites, postganglionic cholinergic sympathetic and parasympathetic muscarinic sites, skeletal muscle nicotinic sites, and central nervous system sites.

Signs and Symptoms

The clinical syndrome of muscarinic acetylcholinesterase inhibition is commonly called the SLUDGE syndrome. This stands for salivation, lacrimation, urinary incontinence, defecation, gastroenteritis, and emesis. Because parasympathetic hyperstimulation of end organs usually is predominant, the usual clinical findings may include miotic pupils, lacrimation, rhinorrhea, salorrhea, vomiting, diarrhea, and urinary incontinence. Bradycardia is commonly mentioned as a classic sign of acetylcholinesterase poisoning, but the increased release of norepinephrine from postganglionic sympathetic neurons precipitated by excess cholinergic activity at sympathetic ganglia may result in normal or even tachycardic heart rates (nicotinic effect). Sympathetic hyperactivity can cause diffuse diaphoresis, although this response is mediated by cholinergic receptors at both preganglionic (nicotinic) and postganglionic (muscarinic) sites.

One additional clue that an organophosphorous compound may be implicated in an acute poisoning is the presence of a characteristic strong, rancid odor on the patient’s clothing, breath, or even vomitus. This fetid odor is a result of the organophosphorous compound and the hydrocarbon solvents usually present.

Complications

Pulmonary hypersecretion, or bronchorrhea, is the usual mechanism of early morbidity and mortality.

The obstruction of upper and lower airways and the potential intrusion of these bronchial secretions into alveolar sacs produce the hypoxia that is the primary concern in the initial stages of poisoning.
Later, the effect of nicotinic hyperstimulation of skeletal muscle determines the ultimate morbidity and mortality of acetylcholinesterase inhibitors. Signs of skeletal muscle hyperactivity include involuntary twitches, fasciculations, and hyperactive reflexes. Unfortunately, muscle hyperactivity eventually gives way to muscle fatigue, including the respiratory musculature and particularly the diaphragm. Although acetylcholinesterase inhibitors may produce direct toxic effects on the central nervous system, neurologic signs of confusion, combativeness, seizures, and coma are primarily the result of hypoxia and other complications of the pulmonary and muscular effects of these agents.

Diagnostic Strategies

The diagnosis of poisoning by cholinesterase inhibitors is confirmed by demonstrating reduced levels of cholinesterase activity in plasma (serum) and erythrocytes. Unfortunately, many hospital laboratories do not have the in-house capability to determine cholinesterase levels. Most patients with a significant, acute exposure demonstrate sharply reduced to absent plasma cholinesterase levels within a few hours of exposure. Any patient who has a full-blown cholinergic syndrome should be treated empirically without waiting for laboratory confirmation of decreased cholinesterase activity.

Known or suspected exposure to cholinesterase inhibitors should be confirmed by ordering both plasma and erythrocyte (RBC) cholinesterase levels. In acute exposures, the plasma cholinesterase levels fall first, with decreases in RBC cholinesterase levels lagging behind. Patients with chronic exposures may demonstrate only reduced RBC cholinesterase activity, and their normal plasma cholinesterase levels may impart a false sense of security. The true reflection of depressed cholinesterase activity is found in the RBC activity, and even a very mild acute exposure may result in severe clinical poisoning in these individuals. Red blood cell cholinesterase levels recover at a rate of 1% per day in untreated patients and take about 6 to 12 weeks to normalize, whereas plasma cholinesterase levels may recover in 4 to 6 weeks.

Other ancillary studies should be geared toward the evaluation of pulmonary, cardiovascular, and renal function, and fluid and electrolyte balance.

Differential Diagnosis

Few toxins or other clinical conditions produce the same symptoms as acetylcholinesterase inhibitors. One species of mushroom, *Amanita muscaria*, has historically been mentioned in the differential diagnosis, but this species actually contains alkaloids that usually produce an anticholinergic (antimuscarinic) syndrome. A variety of conditions that induce excessive vagal responses (e.g., inferior wall myocardial infarction) may also produce some signs suggestive of acetylcholinesterase inhibition, but other symptoms should make the primary cause apparent.

Management

Treatment of poisoning with acetylcholinesterase inhibitors is directed toward four goals: (1) decontamination, (2) supportive care, (3) reversal of acetylcholine excess at muscarinic sites, and (4) reversal of toxin binding at active sites on the cholinesterase molecule.

Decontamination is particularly important in cases of dermal exposure; removal and destruction of clothing and thorough flushing of exposed skin may limit absorption and subsequent toxicity. All caregivers should use universal precautions including eyeshields, protective clothing, and nitrile or butyl rubber gloves, if available. In the case of ingestion, standard GI decontamination procedures are of questionable benefit because of the rapid absorption of these compounds. Profuse vomiting and diarrhea are seen early in ingestion and may limit or negate any beneficial effect of additional GI decontamination. Equipment may be washed with a 5% hypochlorite solution to inactivate the cholinesterase inhibitor. Because morbidity primarily results from airway and respiratory failure, supportive care should be directed primarily toward airway management, including suctioning of secretions and vomitus, oxygenation, and, when necessary, ventilatory support. Succinylcholine can be used for intubation but may have extremely prolonged duration. It is preferable to use a competitive neuromuscular blocking agent such as
rapacuronium or rocuronium for rapid sequence intubation in these patients, while recognizing that increased dosing may be necessary. The cardiovascular complications that occur in this setting rarely require specific therapy.

The definitive treatment of acetylcholinesterase inhibition starts with the administration of atropine. A competitive inhibitor of acetylcholine at muscarinic receptor sites, atropine will reverse the clinical effects of cholinergic excess at parasympathetic end organs and sweat glands. Large doses of atropine may be required, and the usual regimen is 2 to 5 mg intravenously every 5 minutes until control of mucous membrane hypersecretion is attained and the airway clears. If intravenous access is not immediately available, the atropine may be administered intramuscularly. Patients may require as much as 200 to 500 mg of atropine intravenously during the first hour, followed by prolonged continuous infusions of 50 to 100 mg/hr to maintain adequate secretion control. The doses required will produce marked tachycardia and mydriasis, which are two of the early signs of atropinization but are not indications to stop atropine administration. The end-point of atropinization is drying of respiratory secretions. Adequate use of atropine should prevent patients from literally “drowning in their own secretions,” the primary cause of early death. Atropine is not active at nicotinic sites and will not reverse the skeletal muscle effects (e.g., muscle fatigue and respiratory failure).

The second part of acetylcholinesterase inhibition treatment is the use of pralidoxime (Protopam, 2-PAM) to break up the organophosphate-acetylcholinesterase complex and restore cholinesterase activity at both muscarinic and nicotinic sites. The usual starting dose of pralidoxime is 1 to 2 gm IV, and additional doses may be given based on clinical response and serial cholinesterase levels. The medication may be given in a bolus of 1 to 2 g intravenously over 30 to 60 minutes every 4 to 8 hours, or as a continuous infusion ranging from 500 to 1000 mg/hr. The infusion may be continued for several days with no apparent adverse effects attributable to the pralidoxime; however, rapid administration has led to hypertension and a transient reversible neuromuscular blockade. The ideal dose of pralidoxime should be determined by monitoring the clinical condition of the patient and serial cholinesterase levels. Patients suffering from agitation, seizures, and coma should be treated with adequate doses of lorazepam or diazepam after the airway has been secured.

Sarin, soman, tabun, and VX are nerve agents that might be used in a terrorist attack. These agents have important differences from the common organophosphorous insecticides. VX is an oily but highly toxic agent with low volatility. It will not readily vaporize and, because its risk of inhalation is low, exposure will be predominately percutaneous. The other agents will be mostly dispersed into the air with inhalation as the predominate route of exposure. These agents will not require the same extremely large doses of atropine but will require pralidoxime. The U.S. military has preloaded Mark I antidote syringes containing 2 mg atropine and 600 mg of pralidoxime for intramuscular use. In mild symptomatic exposures one kit is given, moderate exposures receive two kits, and severe exposures get three kits. Any patient who requires three kits or has seizures also receives 10 mg of diazepam intramuscularly. Four milligrams of lorazepam is a reasonable alternative. These recommendations are well researched and are reasonable suggestions for civilian use.

Reference: