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Anticholinesterase (Organic Phosphorus and Carbamate) Pesticide Poisoning

Introduction

Organic phosphorus (OP) and carbamate compounds are some of the most widely utilized pesticides in the world. Globally, these agents may kill more people each year than acute poisoning by any other chemical. These pesticides contribute to thousands of deaths annually in Asia, where some of the most toxic agents are applied in large amounts and suicidal ingestions are common. In California, several hundred exposures to organic phosphorus and carbamate pesticides are reported to the California Poison Control System (CPCS) each year, with 1-2 resulting fatalities. More strict control over the most toxic of these chemicals in the United States and other countries has likely resulted in fewer severe cases of exposure in recent years, and possibly fewer deaths. However, these insecticides still rank as the most frequently lethal insecticides in use in the United States, and among the most lethal intentional poisonings overall. Severe occupational or unintentional poisoning also occurs where these insecticides are used, but deaths are generally less common.

Case presentation

A 30 year old suicidal man was brought by relatives to the emergency department (ED) after drinking two cups of 50% parathion about 3 hours earlier. The patient was awake but confused and extremely diaphoretic. His initial vital signs in the ED were: blood pressure 200/110 mm Hg; pulse 105 beats/min; respiratory rate 24 breaths/min; temperature 98.6°F; and oxygen saturation 94% on room air. Physical examination showed mid-sized pupils, minimal crackles in all lung fields, and copious vomiting and diarrhea. The patient was drooling between episodes of vomiting.

On initial evaluation his airway was patent and he was not in immediate respiratory distress. He was placed on oxygen by face mask, put on a cardiac monitor, an intravenous (IV) line was inserted and 2 mg atropine administered. Even with supplemental oxygen and atropine given, the patient's oxygen saturation began to fall soon after arrival in the ED. His heart rate also rapidly increased to 120 beats/min, and

an ECG demonstrated a prolonged QTc interval. A portable chest radiograph showed bilateral pulmonary edema. The poison center was contacted and recommended administration of more atropine and pralidoxime. After an additional 4 mg atropine and pralidoxime 1 g IV, his breath sounds improved. His oxygenation continued to fall, and he began coughing up pink-tinged, frothy sputum. He continued to have large amounts of vomiting and diarrhea. A pralidoxime bolus of 1 g was administered IV over 15 minutes and an infusion at 500 mg/h was initiated. The poison center also advised giving additional 2 mg atropine doses every 5–15 minutes as needed to control his secretions.

Although the emesis, diarrhea, and bronchorrhea diminished after a total of 25 mg of atropine, the clinicians elected to intubate the patient. His oxygen saturation following intubation was 98% on 100% FIO₂. He was transferred to the intensive care unit (ICU). Toxicology screening including acetaminophen and salicylate concentrations was negative.

In the ICU, the pralidoxime infusion was continued at 500 mg/h, and atropine was administered intermittently throughout the first 24 hours of admission for a total dose of 30 mg. The chest radiograph improved over the first 24 hours. His ECG gradually improved by the second day, with a heart rate of 105, and normalization of his QTc interval.

On hospital day 2, his sedation was terminated and he was extubated. His nausea and vomiting had largely improved, and no further frothy sputum was observed. Cholinesterase measurements sent initially showed virtually no detectable red blood cell (RBC) or butyrylcholinesterase (plasma) activity. He was transferred to a step-down unit for observation, and did not require any further atropine that day. The pralidoxime infusion was maintained at 500 mg/h.

On hospital day 3, the patient reported feeling much better. His pralidoxime infusion was stopped and he was evaluated by psychiatry and transferred to the inpatient psychiatric service the following afternoon.

Questions:

1. What is the mechanism of toxicity of OP and carbamate pesticides?
2. What are the most common life-threatening effects of OP and carbamate pesticides?
3. What treatments are most important in managing poisonings by these agents?

Epidemiology

In 2007, Californians reported over 700 exposures to OP and carbamate pesticides to the CPCS. Nationally, more than 15,000 poisonings with these chemicals are reported to poison control centers each year, with five or six fatalities. The World Health Organization (WHO) estimates that at least one million unintentional poisonings and two million suicide attempts occur annually worldwide from these insecticides. However, these figures undoubtedly omit numerous unreported and possibly unrecognized illnesses resulting from lower level environmental exposure to these chemicals.

Most often patients present following unintentional or suicidal ingestion of cholinesterase inhibiting insecticides or after working in areas recently treated with these compounds. Children and adults can develop toxicity while playing in or inhabiting a residence recently sprayed or fogged with OP or carbamate insecticides. Direct dermal contact with certain types of these insecticides may be rapidly poisonous. Outbreaks of mass poisoning have occurred from contamination of crops or food. OP agents have also been used for homicide.

OP and carbamate pesticides are collectively known as anticholinesterase agents due to their activity at cholinergic nerve terminals in the body. Although the term "organophosphate" is traditionally used in clinical practice and in the literature to refer to all phosphorus-containing pesticides that inhibit cholinesterase, phosphates (or phosphoric acids) include compounds in which a P atom is bound covalently to four O atoms; non-phosphate derivatives of phosphoric and phosphonic acids such as phosphonates can also exhibit cholinesterase inhibition. Thus the term organic phosphorus compound may be more inclusive and less misleading.

Pathophysiology

Acetylcholine (ACh) is a neurotransmitter found at both parasympathetic and sympathetic ganglia, skeletal neuromuscular junctions, terminal junctions of all postganglionic parasympathetic nerves, post-ganglionic sympathetic fibers to most sweat glands, and at some nerve endings within the central nervous system. As the axon terminal is depolarized, vesicles containing ACh fuse with the nerve terminal, releasing ACh into the synapse or neuro-muscular junction. Acetylcholinesterase (AChE) is an enzyme that hydrolyzes ACh into two inert fragments: acetic acid and choline. Under normal circumstances, virtually all ACh released by the axon is hydrolyzed almost immediately. Organic phosphorus insecticides and carbamates inhibit numerous carboxylic ester hydrolases within the body, including AChE, plasma or butyrylcholinesterase (pseudocholinesterase), and other nonspecific proteases. AChE is found in human nervous tissue and skeletal muscle, and on erythrocyte (RBC) cell membranes. The end result of cholinesterase inhibition is a build up of ACh in nerve terminals leading to excessive stimulation of cholinergic neurons in the autonomic, peripheral and central nervous systems. Chemical weapons known as "nerve agents" are volatile, rapidly acting cholinesterase inhibiting agents that work similarly to organic phosphorus and carbamate pesticides.

The OP and carbamate pesticides bind to a hydroxyl group at the active site of the AChE enzyme. Part of the OP insecticide is split off during its bonding to AChE, and a stable but slowly reversible bond results between the remaining OP moiety and the enzyme, effectively inactivating the enzyme in a process called "aging." The aged OP-enzyme bond can take days to sever, and de-novo synthesis of the enzyme is usually required for a return of function. The carbamate-enzyme bond does not undergo aging and resolution of clinical toxicity is generally more rapid than with organic phosphorus poisoning.

Clinical presentation

Clinical findings of toxicity from OP and carbamate compounds derive from excessive stimulation of muscarinic and nicotinic cholinergic receptors by ACh in the central and autonomic nervous systems, and at skeletal neuromuscular junctions. A patient with anticholinesterase insecticide poisoning is classically described as unresponsive with pinpoint pupils, muscle fasciculations, diaphoresis, emesis, diarrhea, salivation, lacrimation, urinary incontinence, and an odor of garlic or solvents; however, most clinical presentations are not so typical. The onset of symptoms varies according to the compound, the route, and the degree of exposure. Patients suffering massive ingestions can become symptomatic as quickly as 5 minutes following ingestion, and deaths have occurred within 15 minutes of ingestion. Most victims of acute poisonings become symptomatic within 8 hours of exposure, and nearly all are symptomatic within 24 hours. The longest delays may occur with compounds requiring metabolic activation, such as malathion, or very lipid-soluble agents such as fenthion. Symptoms may last for variable lengths of time, again based on the agent and the circumstances of the exposure. The more lipophilic compounds can cause cholinergic effects for days following oral ingestion.

The effects of excessive ACh on the autonomic nervous system may vary because cholinergic receptors are found in both the sympathetic and parasympathetic nervous systems. Excessive muscarinic activity can be characterized by several mnemonics, including "SLUD" (salivation, lacrimation, urination, defecation) and "DUMBBBELS" (defecation, urination, miosis, bradycardia, bronchospasm, bronchorrhea, emesis, lacrimation, salivation). Of these, miosis may be the most consistently encountered sign, but multiple clinical variations can occur. Bronchorrhea can be so profuse that it mimics pulmonary edema.

Although parasympathetic or muscarinic findings are emphasized in these mnemonics, muscarinic signs may not be clinically evident, except in very severe poisonings. In many cases, parasympathetic findings are offset by excessive autonomic activity from stimulation of nicotinic adrenal receptors (resulting in catecholamine release) and postganglionic sympathetic fibers. Mydriasis is reported in many cases. Sympathetic stimulation may result in hyperglycemia, leukocytosis and urinary retention.

Cardiopulmonary effects are also common with severe poisonings from cholinesterase inhibitors. Increased sympathetic tone is often initially present, and most patients present with a sinus tachycardia, with or without hypertension. Bradycardia with a prolonged PR interval and atrioventricular blocks of various degrees occur as toxicity becomes more severe. QT interval prolongation has been reported in severe cases. The most common pulmonary complications of these compounds are bronchorrhea and bronchoconstriction. Liquid pesticide preparations are usually dissolved in a hydrocarbon-based solvent, frequently resulting in aspiration leading to hydrocarbon-induced pneumonitis.

Acetylcholine stimulation of nicotinic receptors also governs skeletal muscle activity. The effects of excessive cholinergic stimulation at these sites are similar to that of a depolarizing neuro-muscular blocking agent (succinylcholine) initially resulting in fasciculations or weakness. As the severity of poisoning progresses, paralysis ensues.

Paralysis of the respiratory muscles in combination with bronchorrhea, bronchoconstriction, and CNS depression leads to hypoxemia and respiratory arrest, which is the most common cause of death.

Diagnosis

When a patient presents in cholinergic crisis with a history of acute excessive exposure to a cholinesterase inhibitor insecticide, the diagnosis is usually straightforward. However, when the history is unreliable or does not suggest poisoning, the physician must turn to other means to confirm the diagnosis of OP or carbamate insecticide poisoning.

The most reliable laboratory test for confirming cholinesterase inhibition by insecticides measures specific insecticides or active metabolites in biologic tissues. Unfortunately, urine and serum assays for organic phosphorus compounds and their metabolites are available but are rarely obtainable within a reasonable period of time to guide clinical management. Therefore, the most accurate and readily obtainable laboratory testing for these agents relies on surrogate markers for neuronal ACh found in the red blood cell (RBC) and plasma. Butyrylcholinesterase (plasma cholinesterase) is able to metabolize various compounds, including succinylcholine and cocaine. RBCs contain a form of AChE that is structurally similar to the enzyme found in nerve tissue. Inhibition of either RBC cholinesterase or butyrylcholinesterase does not contribute to signs or symptoms of poisoning. Testing the activity of these enzymes only serves as a marker of systemic cholinesterase inhibitor poisoning.

After a significant exposure, butyrylcholinesterase activity usually falls first, followed rapidly by a decrease in RBC cholinesterase activity. The sequence may be highly variable, but by the time patients present with acute symptoms, levels of both cholinesterase activities have usually fallen well below baseline values, and often have fallen below detectable limits.

Butyrylcholinesterase activity usually recovers before RBC cholinesterase activity, often returning to normal within a few days in the absence of a repeat or ongoing exposure. However, butyrylcholinesterase activity is less specific for exposure than is red cell cholinesterase activity. Low butyrylcholinesterase activity can be found in patients with a number of disorders, including malnutrition, hepatic disease, metastatic cancer, and iron deficiency anemia. Oral contraceptives can also cause a measurable decrease in butyrylcholinesterase activity. Additionally, day-to-day variation in the activity of this enzyme in healthy individuals may be as high as 20%.

RBC cholinesterase activity is thought to reflect nervous tissue AChE activity more accurately than butyrylcholinesterase. Because these blood tests are only markers of neuronal enzyme inhibition, individual variation may lead to some patients presenting highly symptomatic after minimal reductions in RBC or butyrylcholinesterase, while others may be asymptomatic after losing 50% activity. The wide range of normal RBC and butyrylcholinesterase activity also allows for patients with high-normal values to suffer significant falls in cholinesterase activity, yet still register near normal levels of

cholinesterase activity on laboratory assay. The most important aspect to consider when interpreting the cholinesterase activity is the comparison of reported laboratory values with baseline values in that individual. Because baseline values are usually unavailable in most cases, laboratories report out a "reference range" of activity. This range is based on the central 95% of values of cholinesterase activity for the general population.

Treatment

The earliest potential causes of death in anticholinesterase poisoning are respiratory failure and hypoxemia that may result from coma and convulsions, nicotinic effects on skeletal muscles (weakness and paralysis) and muscarinic effects on the cardiovascular and pulmonary system (bronchospasm, bronchorrhea, aspiration, bradydysrhythmias, or hypotension.) Therefore primary treatment for a patient exposed to these compounds is directed at ensuring an adequate airway and ventilation, and at reversing excessive muscarinic effects, particularly bronchorrhea. Decontamination of the skin is important in topical exposures but GI decontamination is unlikely to be effective in the majority of cases. Contamination of health care workers with these agents during decontamination procedures is possible but very unlikely when standard barrier protection precautions are undertaken.

Atropine antagonizes ACh at muscarinic cholinergic receptors to reverse excessive secretions, miosis, bronchospasm, vomiting, diarrhea, diaphoresis, and urinary incontinence. For adults with anticholinesterase pesticide poisoning, IV doses should begin with boluses of 1–5 mg. Recommended dosing for children is 0.05 mg/kg up to adult doses depending on the severity of symptoms. Repeat doses of 1–2 mg should be given every 2–3 minutes or more rapidly until stabilization occurs. A reduction in pulmonary secretions is the primary target of atropine therapy. Large cumulative doses of atropine may be required. Tachycardia is *not* a contraindication to atropine therapy. Isolated pulmonary manifestations may respond to administration of nebulized atropine or ipratropium. If atropine-induced antimuscarinic CNS toxicity is present, but peripheral cholinergic findings necessitate the administration of more atropine, glycopyrrolate bromide can be substituted for atropine because its quaternary ammonium structure limits CNS penetration.

Although pesticide-bound AChE undergoes hydrolytic regeneration at a very slow rate, this process can be enhanced by using an oxime medication such as pralidoxime hydrochloride (2-PAM). Pralidoxime is unable to rejuvenate active enzyme from the OP–AChE complex that has undergone aging. Therefore, pralidoxime therapy is most effective if started early in the course of toxicity. The starting dose of pralidoxime for adults is 1–2 g IV and for children 20–40 mg/kg IV, both over 10–15 minutes. A constant infusion of pralidoxime appears to be more effective than bolus dosing in maintaining necessary levels. For adults, a maintenance infusion of 250–500 mg/h is usually recommended, titrating to symptoms, but infusions of up to 8 mg/kg/h or more may be required in some cases. Reports in children suggest using a continuous infusion of 10–20 mg/kg/h after the initial bolus. Side effects of pralidoxime are usually minimal at normal doses. The efficacy of pralidoxime in some anticholinesterase pesticide

poisonings has been questioned in recent studies from other countries, and results may depend on the agent involved in the exposure.

Finally, studies suggest the administration of diazepam or other benzodiazepines may improve outcome in anticholinesterase pesticide poisoning. Besides decreasing the incidence of seizure and resulting CNS damage, there is data to support improved respiratory function and outcome when benzodiazepines are used in conjunction with oximes in severe cases.

Discussion of case questions

1. What is the mechanism of toxicity of OP and carbamate pesticides?

OP and carbamate pesticides cause toxicity by binding to cholinesterase in nerve terminals, inhibiting the breakdown of acetylcholine. The result is excessive stimulation of cholinergic neurons on the autonomic, peripheral and central nervous systems.

2. What is the most common life-threatening effect of OP and carbamate pesticides?

Extreme weakness and paralysis due to cholinergic motor neuron stimulation leading to respiratory arrest is the earliest cause of death in most anticholinesterase pesticide poisonings. Copious pulmonary secretions from muscarinic stimulation can lead to pulmonary edema, aspiration and hypoxia that can also be fatal.

3. What treatments are most important in managing poisonings by these agents?

Airway support with mechanical ventilation may be required as initial therapy in severe cases when paralysis and respiratory arrest are imminent. Atropine should be administered, often in large quantities, to control muscarinic signs and symptoms. Pralidoxime should also be given to patients with symptomatic OP poisoning to help more quickly rejuvenate cholinesterase.

Consultation assistance

Consultation with a specialist in poison information or with a medical toxicologist can be obtained free of charge by calling the California Poison Control System at 1-800-222-1222.

This issue of *CALL US...* was written by Richard F. Clark, MD

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