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Organophosphate Toxicity

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Continuing Education Activity

Most patients exposed to organophosphates come into contact with insecticides. The first organophosphate insecticide was created in the mid-1800s but was not widely used until after World War II. Organophosphates are used as medications, insecticides, and nerve agents as a weapon. Symptoms include increased saliva and tear production, diarrhea, nausea, vomiting, small pupils, sweating, muscle tremors, and confusion. The onset of symptoms is often within minutes, and it can take weeks to disappear. This activity reviews the evaluation and treatment of organophosphate toxicity and the role of the interprofessional team in managing this condition.

Objectives:

- Describe common uses of organophosphates.
- Discuss the signs and symptoms of organophosphate toxicity
- Outline the evaluation of a patient with suspected organophosphate toxicity.
- Summarize the evaluation and treatment of organophosphate toxicity and the role of the interprofessional team in managing this condition.

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Introduction

Most patients exposed to organophosphates come into contact with insecticides. The first organophosphate insecticide was created in the mid-1800s but was not widely used until after World War II. Organophosphates are used as medications, insecticides, and nerve agents as a weapon. Symptoms include increased saliva and tear production, diarrhea, nausea, vomiting, small pupils, sweating, muscle tremors, and confusion. The onset of symptoms is often within minutes, and it can take weeks to disappear.[1][2][3][4][5]

Today, the majority of organophosphate toxicity occurs in farmers and people who work in agriculture, since these agents are heavily used in this industry.

Etiology

Organophosphate pesticide exposure may occur through inhalation, ingestion, or dermal contact. Crops that farmworkers come into contact with that also may include organophosphates such as apples, celery, bell peppers, peaches, strawberries, nectarines, grapes, spinach, lettuce, cucumbers, domestic blueberries, and potatoes.

The severity of the symptoms depends on the amount ingested, route of absorption, and rate of metabolic breakdown of the insecticide.

Epidemiology

An estimated 3 million or more people worldwide are exposed to organophosphates each year, accounting for about 300,000 deaths. In the United States, there are around 8000 exposures per year with very few deaths. While most often the exposure occurs from an agricultural pesticide, there are household items, such as ant and roach spray, that also contain organophosphate compounds.

Pathophysiology

The key feature of organophosphate insecticides is the inhibition of carboxyl ester hydrolases, chiefly inhibition of acetylcholinesterase (AChE). This enzyme plays a vital role in the breakdown of the neurotransmitter acetylcholine, which is found in both the peripheral and central nervous systems.

The organophosphate insecticide inactivates AChE by phosphorylating the serine hydroxyl group on the enzyme. This is followed by the accumulation of acetylcholine which then overstimulates the nicotinic and muscarinic receptors.

Toxicokinetics

Organophosphate molecules can be absorbed via the skin, inhalation, or in the gastrointestinal tract. Once absorbed, the molecule binds to an acetylcholinesterase molecule in red blood cells, thus making the enzyme inactive. This leads to an overabundance of acetylcholine within synapses and neuromuscular junctions. Overstimulation of nicotinic receptors found at neuromuscular junctions can lead to fasciculations and myoclonic jerks. This eventually leads to flaccid paralysis because of the depolarizing block. Nicotinic receptors also are found in the adrenal glands, which may cause hypertension, sweating, tachycardia, and leukocytosis with a left shift.[6][7][8][9]

Organophosphate poisoning also produces symptoms based on its action at muscarinic receptors. These effects are usually slower than the nicotinic receptors because the effects occur via a G-protein-coupled receptor mechanism. Muscarinic receptors are found in the parasympathetic and sympathetic nervous systems. Sweat glands within the sympathetic nervous system get overstimulated and cause large amounts of sweating. The parasympathetic effects of organophosphate poisoning can be seen in multiple systems, including the heart, exocrine glands, and smooth muscles. At some point, which is different for each specific compound, the acetylcholinesterase-organophosphate compound undergoes a process called aging. This is a conformational change that renders the enzyme resistant to reactivation, making some treatment options useless.

History and Physical

Organophosphates stimulate both the sympathetic and parasympathetic nervous systems. A typical clinical scenario will involve symptoms of overstimulation of the parasympathetic system. An exception is in children, as they typically have a predominance of symptoms mediated by nicotinic receptors.

There are a couple of mnemonics that are helpful to remember the symptoms of organophosphate poisonings and the receptor that is responsible.

For nicotinic signs of acetylcholinesterase inhibitor toxicity, think of the days of the week:

- Monday = Mydriasis
- Tuesday = Tachycardia
- Wednesday = Weakness
- Thursday = Hypertension
- Friday = Fasciculations.

The more common mnemonic that captures the muscarinic effects of organophosphate poisonings is DUMBELS:

- D = Defecation/diaphoresis
- U = Urination
- M = Miosis
- B = Bronchospasm/bronchorrhea
- E = Emesis
- L = Lacrimation
- S = Salivation.

Additional symptoms can include anxiety, confusion, drowsiness, emotional lability, seizures, hallucinations, headaches, insomnia, memory loss, and circulatory or respiratory depression. When death occurs, the most common reason is respiratory failure stemming from bronchoconstriction, bronchorrhea, central respiratory depression or weakness/paralysis of the respiratory muscles. If the patient survives the acute poisoning, there are other long-term complications.

Intermediate neurologic symptoms typically occur 24 to 96 hours after exposure. Symptoms include neck flexions, weakness, decreased deep tendon reflexes, cranial nerve abnormalities, proximal muscle weakness, and respiratory insufficiency. With supportive care, these patients can have a complete return to normal neurologic function within 2 to 3 weeks. Another later complication is neuropathy. This is linked to very specific organophosphate compounds that contain chlorpyrifos. Most commonly this starts as stocking-glove paresthesia and progresses to symmetric polyneuropathy with flaccid weakness that starts in the lower extremities and progresses to include the upper extremities.

Those who survive may also develop the following neuropsychiatric deficits:

- Confusion
- Impairment in memory
- Lethargy
- Psychosis
- Irritability
- Parkinson like symptoms

Evaluation

Diagnosis of acute or chronic organophosphate poisoning is strictly clinical. You must have a high clinical suspicion for organophosphate poisoning when no history of exposure or ingestion is known. Some organophosphates have a distinct garlic or petroleum odor that may help in diagnosis. If organophosphate poisoning is on the differential but not confirmed, a trial of atropine may be employed. If symptoms resolve after atropine, this increases the likelihood of an acetylcholinesterase inhibitor poisoning. Some labs can directly measure red blood cell acetylcholinesterase activity, but these are often sent out to labs that are not available in a timely enough fashion to guide therapy.

Today there is a portable test that can measure AChE in red blood cells within minutes. The blood must be drawn before pralidoxime is administered. The red cell AChE correlates with neuronal AChE and can be used to determine response to therapy.

Plasma AChE is not used as it is a liver acute-phase protein that circulates in the blood and has no correlation to symptoms. Plus, the levels of plasma AChE do vary due to infection, pregnancy, and medical illness.

Other blood work that should be ordered includes CBC, glucose levels, troponin, liver and renal function, and arterial blood gas.

The ECG will reveal sinus bradycardia due to parasympathetic activation.

Treatment / Management

The first step in the management of patients with organophosphate poisoning is putting on personal protective equipment. These patients may still have the compound on them, and you must protect yourself from exposure. Secondly, you must decontaminate the patient. This means removing and destroying all clothing because it may be contaminated even after washing. The patient's skin needs to be flushed with water. Dry agents such as flour, sand, or bentonite also can be used to decontaminate the skin. In the case of ingestion, vomiting and diarrhea may limit the amount of substance absorbed but should never be induced. Activated charcoal can be given if the patient presents within 1 hour of ingestion, but studies have not shown a benefit.

Airway control is vital. In some patients, intubation may be required due to bronchospasm, seizures, or bronchorrhea. During intubation, succinylcholine must be avoided as it may prolong the paralysis. The reason is that succinylcholine is also degraded by acetylcholine esterase.

Good intravenous access, cardiac monitoring, and pulse oximetry are the standard of care.

The definitive treatment for organophosphate poisoning is atropine, which competes with acetylcholine at the muscarinic receptors. The initial dose for adults is 2 to 5 mg IV or 0.05 mg/kg IV for children until reaching the adult dose. If the patient does not respond to the treatment, double the dose every 3 to 5 minutes until respiratory secretions have cleared and there is no bronchoconstriction. In patients with severe poisoning, it may take hundreds of milligrams of atropine given in bolus or continuous infusion over several days before the patient improves.

Pralidoxime (2-PAM) also should be given to affect the nicotinic receptors since atropine only works on muscarinic receptors. Pralidoxime works by reactivating the phosphorylated AChE by binding to the organophosphate. However, to work, it has to be given within 48 hours of the poisoning. The agent does not depress the respiratory center and can be combined with

atropine. Evidence about the use of oximes to treat organophosphate poisoning is inconsistent, and interpretation is difficult. Until this is better understood and other treatments become available, all patients poisoned with organophosphorus agents should be treated with an oxime.

Atropine must be given before 2-PAM to avoid worsening of muscarinic-mediated symptoms. A bolus of at least 30 mg/kg in adults or 20 to 50 mg/kg for children should be given over 30 minutes. Rapid administration can cause cardiac arrest. After the bolus, a continuous infusion of at least 8 mg/kg/hr for adults and 10 to 20 mg/kg/hr for children should be started and may be needed for several days.[10][11]

Patients with seizures may benefit from benzodiazepines.

Differential Diagnosis

- Gastroenteritis
- Myasthenia gravis
- Guillain Barre syndrome
- Botulism
- Mushroom toxicity
- Nicotine toxicity

Prognosis

Globally, organophosphate insecticides have mortality rates that vary from 2 to 25%. The most common insecticides involved in death are fenitrothion, dichlorvos, malathion, and trichlorfon. The most common cause of death is respiratory failure.

Postoperative and Rehabilitation Care

Because of the risk of recurrent symptoms and respiratory distress, patients should be hospitalized and observed for at least 48 hours in an intensive care setting. Those who remain asymptomatic after 12 hours may be discharged.

Enhancing Healthcare Team Outcomes

The diagnosis and management of organophosphate poisoning are done with an interprofessional team that consists of an emergency department physician, poison control, nurse practitioner, anesthesiologist, intensivist, and other specialists depending on organ system involvement. The key is to prevent further absorption via the skin, eyes, or lungs. The pharmacist must ensure that the patient is on no other medication that can exacerbate the cholinergic crises. In addition, the pharmacist should be aware that in organophosphate toxicity, hundreds of milligrams of atropine may be required.

The treatment should follow the trauma protocol with the first emphasis on the airways. Symptomatic patients need to be monitored in the ICU. Both atropine and pralidoxime can be used in symptomatic patients but close monitoring is necessary. The outlook for most patients is excellent.[12] [Level 5]

Review Questions

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