ToxTalks:

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

In Partnership with the UVA Division of Medical Toxicology – Department of Emergency Medicine

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Acephate

Ortho® Orthene Fire Ant Killer

Acephate is an organophosphate that is available most commonly as a "fire ant killer" (Orthene®) and has been associated with cases of toxicity in the U.S. Toxicity can occur through oral, inhalation and dermal exposure. Though an uncommon exposure, ingestions in large amounts such as suicide attempts can present with significant toxicity, highlighting the importance for clinicians to understand recognition and management of organophosphate toxicity.

Mechanism of Action

Acetylcholine is a neurotransmitter found at sympathetic and parasympathetic ganglia, postganglionic sympathetic and parasympathetic nerves, and neuromuscular junctions. When the nerve is depolarized, vesicles containing acetylcholine fuse to the terminal, releasing acetylcholine into the synapse or neuromuscular junction. The acetylcholine binds to the postsynaptic receptor, and after a period of time is broken down and removed by acetylcholinesterase.

Acephate is an organophosphate insecticide metabolized in a minor pathway to a more active compound, methamidophos. The oral LD50 for acephate is 1.4 g/kg in male rats, and 1.0 g/kg in female rats.

Organophosphates bind to acetylcholinesterase, inhibiting the enzyme. This causes a buildup of acetylcholine in the terminal as it is no longer able to be broken down by acetylcholinesterase. This will result in an excess of cholinergic stimulation, both nicotinic and muscarinic, via excess acetylcholine available to bind to these receptors. If organophosphates remain bound to the acetylcholinesterase enzymes, a process called "aging" occurs which results in an irreversible inhibition of the acetylcholinesterase. After aging occurs, pralidoxime (2-PAM) will no longer reverse acephate and recovery will require new acetylcholinesterase synthesis.

Clinical Effects

Central Nervous System

The central nervous system effects of organophosphate toxicity are considered to be a major factor leading to the death of the intoxicated patient. Cholinergic receptors are found throughout the central nervous system, with highest concentrations within the reticular activating system, basal ganglia, limbic system, cortical and cerebellar

projections, the retina, and within the ventral and dorsal synapses of the spinal cord. Because of the widespread presence of these receptors, organophosphate poisoning can produce a large variation in neurological signs and symptoms. Headache, vertigo, paresthesias, and anxiety may all occur. Centrally mediated respiratory failure can occur resulting in apnea. A rapidly progressive decrease in the level of consciousness resulting in coma is seen with the time from exposure to coma reported as fast as a few minutes. Grand mal seizures are a documented and a dreaded result of organophosphate exposure. The mechanism of this seizure activity is due to multiple effects on neurotransmitters, with excessive stimulation of cholinergic neurons, stimulation of glutamate (NMDA) excitatory neurotransmitter receptors, and antagonism of GABA mediated systems all having been suggested to play a role. Neuronal injuries are strongly associated with organophosphate induced seizures.

Respiratory

The development of respiratory failure is typically a triad of increased airway resistance, neuromuscular failure, and depression of the central respiratory centers. The organophosphates can result in profuse watery nasal discharge, nasal hyperemia, marked salivation, and bronchorrhea. Weakness of the muscles of the tongue and pharynx has been documented and can lead to upper airway obstruction. Laryngeal muscle paralysis may also occur resulting in vocal cord dysfunction and subsequent stridor. The lower respiratory tract may develop bronchorrhea and bronchoconstriction resulting in a prolonged expiratory phase, cough and wheezing. As systemic absorption occurs, respiratory muscle weakness ensues.

Cardiovascular

The cardiovascular effects from organophosphate poisoning are variable and can be caused by either direct cholinergic effects at the heart or nicotinic effects at the autonomic ganglia. Cardiotoxicity resulting from acetylcholinesterase inhibitors has been divided into three phases. Initially, a period of intense sympathetic activity results in sinus tachydysrhythmias with or without hypertension. Victims may subsequently develop bradydysrhythmias, prolongation of the PR interval, atrioventricular blocks, and hypotension as parasympathetic tone predominates. The third phase occurs with QT prolongation and possible progression to polymorphous ventricular tachycardia (torsades de pointes). The above phases can occur at any time in the poisoned victim and do not necessarily follow any specific progression.

Musculoskeletal

Somatic muscular activity is initiated at nicotinic receptors at motor end plates. With early or minimal exposure to organophosphate, symptoms may be vague and consist of muscular weakness and difficulty with ambulation. With increasing exposure, these agents resemble succinylcholine in that they cause muscular fasciculations and subsequent paralysis.

Ophthalmologic
The organophosphates may cause constriction of both the sphincter muscle of the iris and the ciliary muscle of the lens as well as stimulation of the lacrimal gland. As a result, lacrimation and miosis result. Dark adaptation is lost due to both the pupils' inability to dilate. Patients will frequently complain of eye pain, headache, nausea and vomiting due to ciliary spasm that is exacerbated by attempting to focus on close objects.

Dermal
The dermal sweat glands are innervated by sympathetic muscarinic receptors. When these receptors are stimulated, profuse sweating occurs.

Gastrointestinal
Muscarinic receptors stimulate salivary gland secretion, gastric parietal cell acid and chief cell pepsinogen release, pancreatic secretion, gallbladder contraction, small and large intestinal goblet cell secretion, and decreased intestinal ion and water absorption. In addition, gastric and intestinal motility increases and reflex anal sphincter tone relaxes. As a result, profuse watery salivation and gastrointestinal hyperactivity with resultant nausea, vomiting, abdominal cramps, tenesmus, and uncontrolled defecation are characteristic features of systemic acetylcholinesterase blockade.

Genitourinary
Cholinergic stimulation of the detrusor muscle causes contraction of the urinary bladder. It also causes the trigone and sphincter muscles to relax. The overall effect is involuntary urination with systemic organophosphate poisoning.

Management
1. Airway protection
2. Decontamination: removal of contaminated clothing, wash skin
3. Antidotes administration:
    a. Atropine is an antimuscarinic agent that is a mainstay of treatment in organophosphate poisoning. Treatment with atropine is focused on reversing the respiratory effects, namely the bronchorrhea and bronchospasm associated with organophosphate toxicity. Atropine doses can be given in 2 mg aliquots with doubling of the dose every 5 minutes until reversal of bronchorrhea/bronchospasm. Heart rate should not guide atropine dosing as tachycardia can be present in organophosphate toxicity as a result of nicotinic stimulation and its presence is not a contraindication to dosing. As atropine is an antimuscarinic agent, it will not resolve the muscle weakness caused by nicotinic stimulation.
    b. Pralidoxime (2-PAM) works by reactivating acetylcholinesterase before aging and should be given immediately to any symptomatic patient. Initial dosing should start at 1 gm intravenous in 100 mL of normal saline over 15 minutes. If given IM, IM dosing for adults would be 600mg IM x1 then 1200mg IM in 15 minutes if no improvement.
    c. Benzodiazepines are indicated in organophosphate poisoning in the setting of seizures and should be titrated to seizure cessation.

Summary
Acephate is a relatively weak cholinesterase inhibitor in comparison to other organophosphate pesticides, but remains available for purchase in the United States as an industrial pesticide and most commonly in the form of "fire ant killer" Orthene. It is less likely to cause symptoms with mild exposures due to its relatively weak inhibition of acetylcholinesterase, but with sufficient doses, such as intentional ingestions, it has been associated with significant toxicity. As an organophosphate, it can cause a diffuse array of clinical effects. Treatment is focused on reducing respiratory secretions with atropine and regenerating acetylcholinesterase enzyme with pralidoxime (2-PAM). The Blue Ridge Poison Center can assist in management of these complex cases: 1-800-222-1222.