



Organophosphate Poisoning

Introduction

Organophosphates (OP) have been used as pesticides (Figure 1), weapons, and medicines for decades. They are one of the leading causes of morbidity and untimely deaths in many developing nations.¹⁻⁴ Exposures usually arise from agricultural or occupational use and intentional self-harm.²⁻⁶ OP irreversibly bind to acetylcholinesterase (AChE), the enzyme that metabolizes acetylcholine (ACh). Toxicity occurs from excess accumulation of acetylcholine, an important neurotransmitter in the autonomic nervous system, central nervous system, and neuromuscular junction.³⁻⁶ The clinical course of an acute organophosphate poisoning can be quite severe, therefore early diagnosis and appropriate interventions are necessary to avoid a poor outcome.³

Pharmacokinetics and Pharmacology

OP are readily absorbed through the gastrointestinal tract, skin, and lungs and peak concentrations occur in minutes to hours. These agents are extensively metabolized in the liver to both active and inactive metabolites that are subsequently excreted by the kidney. The elimination half-life for most agents is on the order of hours. Agents that are more fat-soluble (e.g., dichlofenthion) have a longer elimination phase on the order of days.

Organophosphates irreversibly inhibit CNS AChE and plasma pseudocholinesterase leading to increased availability of acetylcholine and over-stimulation of cholinergic synapses in the CNS, autonomic nervous system, and at neuromuscular junctions.³⁻⁵ The binding affinity for the enzyme differs among organophosphate compounds and undergoes a process of "aging" where the affinity increases with time and eventually becomes irreversible. This aging process is complete in minutes to several days depending on the agent.

Toxicology

Acute Cholinergic Crisis

Acute toxic exposures to organophosphates cause excess accumulation of acetylcholine at synapses. Classic cholinergic symptoms derived from the muscarinic receptor over-stimulation are remembered via the mnemonics SLUDGE: Salivation, Lacrimation, Urination, Defecation/Diaphoresis, Gastric secretions, and Emesis; or DUMBELS: Defecation, Urination, Miosis, Bronchorrhea,

Bradycardia, Emesis, Lacrimation, and Salivation/Seizures/Sweating. Nicotinic effects are remembered via the mnemonic MTWHF: Mydriasis (rare), Tachycardia, Weakness, Hypertension, and Fasciculations.^{5,7} The most life-threatening symptoms associated with an acute poisoning are bradyarrhythmias, bronchospasm, muscle weakness, and bronchorrhea (Table 1).^{5, 7, 8}

Central nervous system effects are common in organophosphate exposures. The seizures are thought to be initiated through excess cholinergic stimulation in the brain.

"Intermediate Syndrome"

Controversy exists as to the etiology of this syndrome and even whether it is truly a separate entity. Proposed hypotheses include insufficient antidote (oxime) therapy during the acute cholinergic phase, down-regulation of cholinergic receptors, delayed absorption, or redistribution of sequestered organophosphates from tissue.^{5,9}

The onset of the intermediate syndrome occurs approximately 24-96 hours after apparent recovery from the acute cholinergic crisis and before the onset of delayed neuropathies. It occurs in 10-50% of patients recovering from acute cholinergic toxicity. It is characterized by respiratory insufficiency, proximal muscle weakness, cranial nerve palsies, and marked decrease in neck flexion strength. Distal limb strength may be unimpaired. Ankle and knee reflexes are often diminished or absent. Upper limb reflexes may occasionally be impaired.^{5,7-9}

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Although there does not appear to be any discernible order to the onset of neurological manifestations, Senanayake described an ordered resolution of symptoms. Symptoms resolved as follows; palatal, facial, and external ocular cranial nerve palsies, followed by a decrease in respiratory difficulty and a return of proximal limb strength. The last symptom to resolve was neck flexor weakness.^{5,10} The duration of the intermediate syndrome has varied from 5-18 days from the onset of symptoms.^{5,8,10}

Another distinguishing feature of the intermediate syndrome is that treatment with atropine or pralidoxime do not result in symptomatic improvement.^{5,9}

Organophosphate-Induced Delayed Polyneuropathy (OPIDN)

Delayed onset peripheral neuropathy has been noted with some, but not all OP.¹¹ Triaryl and dialkyl organophosphates such as tri-ortho-cresyl phosphate (TOCP) and chlorpyrifos are the agents most likely to be associated with this effect.⁸ The development of this syndrome is not related to the inhibition of AChE or severity of cholinergic symptoms. OPIDN is a result of phosphorylation and aging of neuropathy protein esterase (NPE), a protein that exists in nervous tissue whose function is poorly understood.^{5,8} TOCP, a weak inhibitor of AChE, was not used historically as a pesticide but rather as a machine lubricant. During 1930-1931, 16,000 people in the United States developed persistent neuropathies (Ginger Jake Paralysis) after drinking "Ginger Jake", a ginger extract that was used as a substitute alcoholic beverage during prohibition. The manufacturer adulterated Ginger Jake with TOCP in an effort to appear compliant with government regulations. In 1959, TOCP was used in Morocco as an adulterant in vegetable oil and 11,000 individuals were stricken with persistent neuropathy.^{5,8}

Symptoms of OPIDN typically develop 1-5 weeks after recovery from an acute, symptomatic OP exposure. It can be either motor or sensory in nature and usually includes lower limb cramps followed by rapidly progressing ascending paralysis. The paralysis is greater in the lower limbs than upper limbs; however severe cases may involve both. Eventually the flaccid paralysis is replaced with hypertonicity and a characteristic gait.^{5,8} Recovery is variable with some patients improving over months and others suffering permanent deficits.

Diagnosis

Diagnosis of organophosphate poisoning is made primarily through history of exposure and documentation of excessive cholinergic symptoms. Laboratory findings of AChE inhibition may be useful to confirm exposure but do not correlate well with the severity of effects.^{5,12} Measurement of red blood cell (RBC) cholinesterase or plasma pseudocholinesterase may confirm the exposure. RBC cholinesterase is a more specific test, whereas, plasma

pseudocholinesterase activity can be affected by malnutrition, oral contraceptive use, iron deficiency anemia, and liver dysfunction. The cholinesterase test results are often difficult to interpret without a baseline value due to the wide range of normal values. Patients can have values within the normal range and still have clinical OP poisoning.

Treatment

The treatments for acute organophosphate poisonings are atropine to block the muscarinic receptors, pralidoxime (2-PAM) to regenerate AChE activity, and benzodiazepine therapy to control seizures.⁸

Atropine is a competitive muscarinic antagonist. The initial dose is 2 to 4 mg in adults and 0.05 mg/kg for children followed by additional doses every 3-5 minutes until pulmonary secretions resolve and mild anticholinergic effects appear.⁵ Atropine may be administered by a continuous infusion of 0.5 to 2.0 mg/hour for adults or 0.025 mg/kg for children, and titrated to response for patients with large atropine requirements. The infusion should be prepared from preservative-free atropine only.

Pralidoxime (2-PAM) works by binding to the AChE/OP moiety and regenerates active AChE. Pralidoxime is most effective in the first 24 hours before "aging" of the AChE/OP complex occurs. Aging occurs at different rates for individual agents, from an aging half-life of 2 minutes for soman to greater than 40 hours for other agents. Therefore, 2-PAM is recommended for any acutely symptomatic patient regardless of time since exposure. The recommended 2-PAM adult IV dose is 1 to 2 gram over 30 minutes (children, 25 to 50 mg/kg) followed by a 500 mg/hour (children 10-20 mg/kg/hr) infusion. Continue treatment until muscle weakness and fasciculations have resolved. Re-emergence of symptoms is possible so patients should be carefully monitored. Seizures should be treated with benzodiazepines. We recommend contacting the Utah Poison Control Center for guidance in continuous antidote administration for symptomatic patients.

Summary

Organophosphates are used as pesticides throughout the world and frequently are the source of illness. Patients present with a range of cholinergic and nicotinic symptoms, which depend on the specific agent and dose. Mainstay treatments include cholinergic antagonism (atropine) and AChE regeneration therapy (2-PAM), along with pulmonary support and the use of benzodiazepines to aid in seizure control. Since delayed effects may occur days to weeks later, patients need continued monitoring following the acute cholinergic crisis.

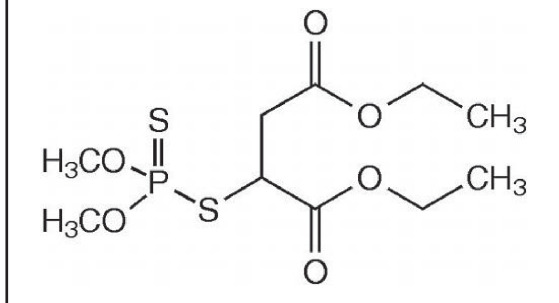
Mike Whipple, PharmD

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Figure 1. Malathion



**Table 1.
Acute Effects of Organophosphate Poisoning**

	Affected Organs	Clinical Presentations
Nervous System		
Autonomic nervous system		
Muscarinic	Gastrointestinal system	Emesis, increased motility, Diarrhea
	Genitourinary system	Urinary incontinence
	Eyes	Lacrimation, Miosis, blurred vision
	Bronchial tree	Bronchorrhea, bronchospasm, wheezing, cough, cyanosis
	Cardiovascular	Bradycardia, hypotension
	Salivary glands	Increased Salivation
	Sudoriferous glands	Diaphoresis
Nicotinic	Adrenal	Increased circulating catecholamines, hypertension, tachycardia
Neuromuscular junction		
Nicotinic	Skeletal muscle	Fasciculation, weakness, paralysis
Central nervous system		
Muscarinic/nicotinic	Brain	Agitation, seizures, CNS depression, coma, confusion, giddiness, Cheyne-Stokes respiration

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New Educational Material Policy

The UPCC offers a variety of poison prevention and awareness educational materials at no cost to the residents of Utah. These materials are offered to poison center callers at the conclusion of a poison center telephone encounter, distributed at health fairs and other community events, at schools and through physician offices, clinics, pharmacies and hospitals. We encourage the use and sharing of these materials. The following is the UPCC's revised policy on distribution of bulk educational materials:

The Utah Poison Control Center (UPCC) has a limited budget for educational materials. To ensure that we have adequate supplies to meet needs, the UPCC will limit distribution of educational materials to quantities of 200 (\$100 value) per quarter. If you have special needs, please contact us. A donation to cover the cost of mailing is greatly appreciated. A suggested donation schedule is as follows:

25 of each item	\$2.00	150 of each item	\$8.00
50 of each item	\$4.00	200 of each item	\$10.00
100 of each item	\$6.00		

If you have needs that extend beyond our policy, don't hesitate to contact us. We will do our best to address specific needs as they arise.

Employment Opportunities

The UPCC has two positions available: one Specialist in Poison Information position and one Specialist in Poison Information-Pharmacist position. You can find out more about these positions on our website at <http://uuhsc.utah.edu/poison/employment> or apply on the University of Utah Human Resource page at <http://www.hr.utah.edu/joblist> (Use keyword "poison" to easily find the job postings.)

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*CSPI denotes Certified Specialist in Poison Information.

Welcome New Employees

The Utah Poison Control Center is pleased to welcome Michael Gearheart, RN, BSN and Michael Donnelly, RN, BSN as Specialists in Poison Information. Michael Gearheart has over 14 years of critical care and emergency medicine nursing experience. Michael Donnelly comes to the UPCC following a long distinguished career as a critical care nurse and nurse manager at the University of Utah Hospital. Please join us in welcoming them to the UPCC team!

Meet the UPCC Staff



Dave Evans received his BS in Pharmacy from the University of Utah in 1974 and his PharmD. from the State University of New York at Buffalo in 1976. He has worked in multiple practice environments including hospital, retail and information systems. Dave has worked on a part time basis at the PCC for many years joining the staff on a full time basis in November of 2004. Interests include gardening, camping and road trips. Favorite poisons are toxic alcohols (ethylene glycol and methanol).

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