CHAPTER 4

Organophosphate Insecticides

HIGHLIGHTS

- Acts through phosphorylation of the acetylcholinesterase enzyme at nerve endings
- Absorbed by inhalation, ingestion, and skin penetration
- Muscarinic, nicotinic & CNS effects

Signs and Symptoms:

- Headache, hypersecretion, muscle twitching, nausea, diarrhea
- Respiratory depression, seizures, loss of consciousness
- Miosis is often a helpful diagnostic sign

Treatment:

- Clear airway, improve tissue oxygenation
- Administer atropine sulfate intravenously
- Pralidoxime may be indicated
- Proceed concurrently with decontamination

Contraindicated:

- Morphine, succinylcholine, theophylline, phenothiazines, reserpine

Since the removal of organochlorine insecticides from use, organophosphate insecticides have become the most widely used insecticides available today. More than forty of them are currently registered for use and all run the risk of acute and subacute toxicity. Organophosphates are used in agriculture, in the home, in gardens, and in veterinary practice. All apparently share a common mechanism of cholinesterase inhibition and can cause similar symptoms. Because they share this mechanism, exposure to the same organophosphate by multiple routes or to multiple organophosphates by multiple routes can lead to serious additive toxicity. It is important to understand, however, that there is a wide range of toxicity in these agents and wide variation in cutaneous absorption, making specific identification and management quite important.

Toxicology

Organophosphates poison insects and mammals primarily by phosphorylation of the acetylcholinesterase enzyme (AChE) at nerve endings. The result is a loss of available AChE so that the effector organ becomes overstimulated by the excess acetylcholine (ACh, the impulse-transmitting substance) in the nerve ending. The enzyme is critical to normal control of nerve impulse transmission from nerve fibers to smooth and skeletal muscle cells, glandular cells, and autonomic ganglia, as well as within the central nervous system (CNS). Some critical proportion of the tissue enzyme mass must be inactivated by phosphorylation before symptoms and signs of poisoning become manifest.

At sufficient dosage, loss of enzyme function allows accumulation of ACh peripherally at cholinergic neuroeffector junctions (muscarinic effects), skeletal nerve-muscle junctions, and autonomic ganglia (nicotinic effects), as well as centrally. At cholinergic nerve junctions with smooth muscle and gland cells, high ACh concentration causes muscle contraction and secretion, respectively. At skeletal muscle junctions, excess ACh may be excitatory (cause muscle twitching), but may also weaken or paralyze the cell by depolarizing the end-plate. In the CNS, high ACh concentrations cause sensory and behavioral disturbances, incoordination, depressed motor function, and respiratory depression. Increased pulmonary secretions coupled with respiratory failure are the usual causes of death from organophosphate poisoning. Recovery depends ultimately on generation of new enzyme in all critical tissues.

COMMERCIAL PRODUCTS

acephate
Orthene
azinphos-methyl+
Gusathion
Guthion
bensulide
Betasan
Lescosan
bomyl+
Swat
bromophos
Nexion
bromophos-ethyl
Nexagan
cadusafos
Apache
Ebufos
Rugby
carbophenothion+
Trithion
chlorethoxyfos
Fortress
chlorfenvinphos
Apachlor
Birlane
chlormephos+
Dotan
chlorphoxim
Baythion-C
chlorpyrifos
Brodan
Dursban
Lorsban
chlorthiophos+
Celathion
coumaphos+
Asuntol
Co-Ral
crotoxyphos
Ciodrin
Cypona
crufomate
Ruelene
cyanofenphos+
Surecide
cyanophos
Cyanox
cythioate
Cyflee
Proban
DEF
De-Green
E-Z-Off D
demeton+
systox
demeton-S-methyl
Duratox
Metasystoxl
dialifor+
Torak
diazinon
dichlorofenthion
VC-13 Nemacide
dichlorvos
DDVP
Vapona
dicrotophos+
Bidrin
dimefos+
Hanane
Pestox XIV
dimethoate
Cygon
DeFend
dioxathion+
Delnav
disulfoton+
Disyston
ditalimfos
edifenphos
endothion+
EPBP
S-Seven
EPN+
ethion
Ethanox
ethoprop
Mocap
ethyl parathion+
E605
Parathion
thiophos
etrimfos
Ekamet
famphur+
Bash
Bo-Ana
Famfos
fenamiphos+
Nemacur
fenitrothion
Accothion
Agrothion
Sumithion
fenophosphon+
Agritox
trichloronate
fensulfothion+
Dasanit
fenthion
Baytex
Entex
Tiguvon
fonofos+
Dyfonate
N-2790
formothion
Anthio
fosthietan+
Nem-A-Tak
heptenophos
Hostaquick
hiometon
Ekatin
hosalone
Zolone
IBP
Kitazin
iodofenphos
Nuvanol-N
isazofos
Brace
Miral
Triumph
isofenphos+
Amaze
Oftanol
isoxathion
E-48
Karphos
leptophos
Phosvel
malathion
Cythion
mephosfolan+
Cytrolane
merphos
Easy off-D
Folex
methamidophos+
Monitor
methidathion+
Supracide
Ultracide
methyl parathion+
E 601
Penncap-M
methyl trithion
mevinphos+
Duraphos
Phosdrin
mipafox+
Isopestox
Pestox XV
monocrotophos+
Azodrin
naled
Dibrom
oxydemeton-methyl
Metasystox-R
oxydeprofos
Metasystox-S
phencapton
G 28029
phenthoate
dimephenthoate
Phenthoate
phorate+
Rampart
Thimet
phosalone
Azofene
Zolone
phosfolan+
Cylan
Cyolane
phosmet
Imidan
Prolate
phosphamidon+
Dimecron
phostebupirim
Aztec
phoxim
Baythion
pirimiphos-ethyl
Primicid
pirimiphos-methyl
Actellic
profenofos
Curacron
propetamphos
Safrotin
propyl thiopyro-
phosphate+
Aspon
prothoate
Fac
pyrazophos
Afugan
Curamil
pyridaphenthion
Ofunack
quinalphos
Bayrusil
ronnel
Fenchlorphos
Korlan
schradan+
OMPA
sulfotep+
Bladafum
Dithione
Thiotepp
sulprofos
Bolstar
Helothion
temephos
Abate
Abathion
terbufos
Contraven
Counter
tetrachlorvinphos
Gardona
Rabon
tetraethyl pyrophos-
phate+
TEPP
triazophos
Hostathion
trichlorfon
Dipterex
Dylox
Neguvon
Proxol

+ Indicates high toxicity. Highly toxic organophosphates have listed oral LD_{50} values (rat) less than or equal to 50 mg/kg body weight. Most other organophosphates included in this table are considered moderately toxic, with LD_{50} values in excess of 50 mg/kg and less than 500 mg/kg.

Organophosphates are efficiently absorbed by inhalation, ingestion, and skin penetration. There is considerable variation in the relative absorption by these various routes. For instance, the oral LD_{50} of parathion in rats is between 3-8 mg/kg, which is quite toxic,[1,2] and essentially equivalent to dermal absorption with an LD_{50} of 8 mg/kg.[2] On the other hand, the toxicity of **phosalone** is much lower from the dermal route than the oral route, with rat LD_{50}s of 1500 mg/kg and 120 mg/kg, respectively.[2] In general, the highly toxic agents are more likely to have high-order dermal toxicity than the moderately toxic agents.

Chemical Classes: To some degree, the occurrence of poisoning depends on the rate at which the pesticide is absorbed. Breakdown occurs chiefly by hydrolysis in the liver; rates of hydrolysis vary widely from one compound to another. In the case of certain organophosphates whose breakdown is relatively slow, significant temporary storage in body fat may occur. Some organophosphates such as diazinon and methyl parathion have significant lipid solubility, allowing fat storage with delayed toxicity due to late release.[3] Delayed toxicity may also occur atypically with other organophosphates, specifically dichlorofenthion and demeton-methyl.[4] Many organothiophosphates readily undergo conversion from thions (P=S) to oxons (P=O). Conversion occurs in the environment under the influence of oxygen and light, and in the body, chiefly by the action of liver microsomes. Oxons are much more toxic than thions, but oxons break down more readily. Ultimately, both thions and oxons are hydrolyzed at the ester linkage, yielding alkyl phosphates and leaving groups, both of which are of relatively low toxicity. They are either excreted or further transformed in the body before excretion.

The distinction between the different chemical classes becomes important when the physician interprets tests from reference laboratories. This can be especially important when the lab analyzes for the parent compound (i.e., chlorpyrifos in its thiophosphate form) instead of the metabolite form (chlorpyrifos will be completely metabolized to the oxon after the first pass through the liver).

Within one or two days of initial organophosphate binding to AChE, some phosphorylated acetylcholinesterase enzyme can be de-phosphorylated (reactivated) by the oxime antidote pralidoxime. As time progresses, the enzyme-phosphoryl bond is strengthened by loss of one alkyl group from the phosphoryl adduct, a process called aging. Pralidoxime reactivation is therefore no longer possible after a couple of days,[5] although in some cases, improvement has still been seen with pralidoxime administration days after exposure.[6]

OPIDN: Rarely, certain organophosphates have caused a different kind of neurotoxicity consisting of damage to the afferent fibers of peripheral and central nerves and associated with inhibition of "neuropathy target esterase" (NTE). This delayed syndrome has been termed organophosphate-induced delayed neuropathy (OPIDN), and is manifested chiefly by weakness or paralysis and paresthesia of the extremities.[7] OPIDN predominantly affects the legs and may

persist for weeks to years. These rare occurrences have been found shortly after an acute and often massive exposure, but in some cases, symptoms have persisted for months to years. Only a few of the many organophosphates used as pesticides have been implicated as causes of delayed neuropathy in humans. EPA guidelines require that organophosphate and carbamate compounds which are candidate pesticides be tested in susceptible animal species for this neurotoxic property.

Three epidemiologic studies with an exposed group and a control group also suggest that a proportion of patients acutely poisoned from any organophosphate can experience some long-term neuropsychiatric sequelae. The findings show significantly worse performance on a battery of neurobehavioral tests, including memory, concentration, and mood, and compound-specific peripheral neuropathy in some cases. These findings are subtle and may sometimes be picked up only on neuropsychologic testing rather than on a neurologic exam.[8-10] Follow-ups of case series have occasionally found some individuals reporting persistent headaches, blurred vision, muscle weakness, depression, memory and concentration problems, irritability, and/or development of intolerance to selected chemical odors.[11-15]

Intermediate Syndrome: In addition to acute poisoning episodes and OPIDN, an intermediate syndrome has been described. This syndrome occurs after resolution of the acute cholinergic crisis, generally 24-96 hours after exposure. It is characterized by acute respiratory paresis and muscular weakness, primarily in the facial, neck, and proximal limb muscles. In addition, it is often accompanied by cranial nerve palsies and depressed tendon reflexes. Like OPIDN, this syndrome lacks muscarinic symptomatology, and appears to result from a combined pre- and post-synaptic dysfunction of neuromuscular transmission. Symptoms do not respond well to atropine and oximes; therefore treatment is mainly supportive.[16,17] The most common compounds involved in this syndrome are methyl parathion, fenthion, and dimethoate, although one case with ethyl parathion was also observed.[17]

Other specific properties of individual organophosphates may render them more hazardous than basic toxicity data suggest. By-products can develop in long-stored malathion which strongly inhibit the hepatic enzymes operative in malathion degradation, thus enhancing its toxicity. Certain organophosphates are exceptionally prone to storage in fat tissue, prolonging the need for antidote for several days as stored pesticide is released back into the circulation. Animal studies have demonstrated potentiation of effect when two or more organophosphates are absorbed simultaneously; enzymes critical to the degradation of one are inhibited by the other. Animal studies have also demonstrated a protective effect from phenobarbital which induces hepatic degradation of the pesticide.[1] Degradation of some compounds to a trimethyl phosphate can cause restrictive lung disease.[18]

Signs and Symptoms of Poisoning

Symptoms of acute organophosphate poisoning develop during or after exposure, within minutes to hours, depending on the method of contact. Exposure by inhalation results in the fastest appearance of toxic symptoms, followed by the gastrointestinal route and finally the dermal route. All signs and symptoms are cholinergic in nature and affect muscarinic, nicotinic, and central nervous system receptors.[5] The critical symptoms in management are the respiratory symptoms. Sufficient muscular fasciculations and weakness are often observed as to require respiratory support; respiratory arrest can occur suddenly. Likewise, bronchorrhea and bronchospasm may often impede efforts at adequate oxygenation of the patient.

Bronchospasm and bronchorrhea can occur, producing tightness in the chest, wheezing, productive cough, and pulmonary edema. A life threatening severity of poisoning is signified by loss of consciousness, incontinence, convulsions, and respiratory depression. The primary cause of death is respiratory failure, and there usually is a secondary cardiovascular component. The classic cardiovascular sign is bradycardia which can progress to sinus arrest. However, this may be superseded by tachycardia and hypertension from nicotinic (sympathetic ganglia) stimulation.[19] Toxic myocardiopathy has been a prominent feature of some severe organophosphate poisonings.

Some of the most commonly reported early symptoms include headache, nausea, dizziness, and hypersecretion, the latter of which is manifested by sweating, salivation, lacrimation, and rhinorrhea. Muscle twitching, weakness, tremor, incoordination, vomiting, abdominal cramps, and diarrhea all signal worsening of the poisoned state. Miosis is often a helpful diagnostic sign and the patient may report blurred and/or dark vision. Anxiety and restlessness are prominent, as are a few reports of choreaform movements. Psychiatric symptoms including depression, memory loss, and confusion have been reported. Toxic psychosis, manifested as confusion or bizarre behavior, has been misdiagnosed as alcohol intoxication.

Children will often present with a slightly different clinical picture than adults. Some of the typical cholinergic signs of bradycardia, muscular fasciculations, lacrimation, and sweating were less common. Seizures (22%-25%) and mental status changes including lethargy and coma (54%-96%) were common.[20, 21] In comparison, only 2-3% of adults present with seizures. Other common presenting signs in children include flaccid muscle weakness, miosis, and excessive salivation. In one study, 80% of cases were transferred with the wrong preliminary diagnosis.[20] In a second study, 88% of the parents initially denied any exposure history. [21]

See the preceding Toxicology section for information regarding the features of the intermediate syndrome and OPIDN.

Confirmation of Poisoning

If poisoning is probable, **treat the patient immediately. Do not wait for laboratory confirmation.**

Blood samples should be drawn to measure plasma pseudocholinesterase and red blood cell AChE levels. Depressions of plasma pseudocholinesterase and/or RBC acetylcholinersterase enzyme activities are generally available biochemical indicators of excessive organophosphate absorption. Certain organophosphates may selectively inhibit either plasma pseudocholinesterase or RBC acetylcholinesterase.[22] A minimum amount of organophosphate must be absorbed to depress blood cholinesterase activities, but enzyme activities, especially plasma pseudocholinesterase, may be lowered by dosages considerably less than are required to cause symptomatic poisoning. The enzyme depression is usually apparent within a few minutes or hours of significant absorption of organophosphate. Depression of the plasma enzyme generally persists several days to a few weeks. The RBC enzyme activity may not reach its minimum for several days, and usually remains depressed longer, sometimes 1-3 months, until new enzyme replaces that inactivated by organophosphate. The above table lists approximate lower limits of normal plasma and RBC cholinesterase activities of human blood, measured by several methods. **Lower levels usually indicate excessive absorption of a cholinesterase-inhibiting chemical.**

APPROXIMATE LOWER LIMITS OF NORMAL PLASMA AND RED CELL CHOLINESTERASE ACTIVITIES IN HUMANS*

Methods	Plasma	RBC	Blood	Whole units
pH (Michel)	0.45	0.55		ÐpH per mL per hr
pH Stat (Nabb-Whitfield)	2.3	8.0		µM per mL per min
BMC Reagent Set (Ellman-Boehringer)	1,875		3,000	mU per mL per min
Dupont ACA	< 8			Units per mL
Garry-Routh (Micro)			Male 7.8 Female 5.8	µM-SH per 3mL per min
Technicon	2.0	8.0		µM per mL per min

* Because measurement technique varies among laboratories, more accurate estimates of minimum normal values are usually provided by individual laboratories.

In certain conditions, the activities of plasma and RBC cholinesterase are depressed in the absence of chemical inhibition. About 3% of individuals have a genetically determined low level of plasma pseudocholinesterase. These persons are particularly vulnerable to the action of the muscle-paralyzing drug succinylcholine (often administered to surgical patients), but not to organophosphates. Patients with hepatitis, cirrhosis, malnutrition, chronic alcoholism, and dermatomyositis exhibit low plasma cholinesterase activities. A number of toxicants, notably cocaine, carbon disulfide, benzalkonium salts, organic mercury compounds, ciguatoxins, and solanines may reduce plasma pseudocholinesterase activity. Early pregnancy, birth control pills, and metoclopramide may also cause some depression. The RBC acetylcholinesterase is less likely than the plasma enzyme to be affected by factors other than organophosphates. It is, however, reduced in certain rare conditions that damage the red cell membrane, such as hemolytic anemia.

The alkyl phosphates and phenols to which organophosphates are hydrolyzed in the body can often be detected in the urine during pesticide absorption and up to about 48 hours thereafter. These analyses are sometimes useful in identifying and quantifying the actual pesticide to which workers have been exposed. Urinary alkyl phosphate and phenol analyses can demonstrate organophosphate absorption at lower dosages than those required to depress cholinesterase activities and at much lower dosages than those required to produce symptoms and signs. Their presence may simply be a result of organophosphates in the food chain.

Detection of intact organophosphates in the blood is usually not possible except during or soon after absorption of a substantial amount. In general, organophosphates do not remain unhydrolyzed in the blood for more than a few minutes or hours, unless the quantity absorbed is large or the hydrolyzing liver enzymes are inhibited.

Treatment

Caution: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while washing pesticide from skin and hair. Vinyl gloves provide no protection.

1. Airway protection. Ensure that a clear airway exists. Intubate the patient and aspirate the secretions with a large-bore suction device if necessary. Administer oxygen by mechanically assisted pulmonary ventilation if respiration is depressed. **Improve tissue oxygenation as much as possible before administering atropine, so as to minimize the risk of ventricular fibrillation.** In severe poisonings, it may be necessary to support pulmonary ventilation mechanically for several days.

2. Atropine sulfate. Administer atropine sulfate intravenously, or intramuscularly if intravenous injection is not possible. Remember that atropine can be administered through an endotracheal tube if initial IV access is difficult to obtain. Depending on the severity of poisoning, doses of atropine ranging from very low to as high as 300 mg per day may be required,[23] or even continuous infusion.[24,25] (See dosage on next page.)

The objective of atropine antidotal therapy is to antagonize the effects of excessive concentrations of acetylcholine at end-organs having muscarinic receptors. Atropine does not reactivate the cholinesterase enzyme or accelerate disposition of organophosphate. Recrudescence of poisoning may occur if tissue concentrations of organophosphate remain high when the effect of atropine wears off. Atropine is effective against muscarinic manifestations, but it is ineffective against nicotinic actions, specifically muscle weakness and twitching, and respiratory depression.

Despite these limitations, atropine is often a life-saving agent in organophosphate poisonings. Favorable response to a test dose of atropine (1 mg in adults, 0.01 mg/kg in children under 12 years) can help differentiate poisoning by anticholinesterase agents from other conditions. However, lack of response, with no evidence of atropinization (atropine refractoriness) is typical of more severe poisonings. The adjunctive use of nebulized atropine has been reported to improve respiratory distress, decrease bronchial secretions, and increase oxygenation.[26]

3. Glycopyrolate has been studied as an alternative to atropine and found to have similar outcomes using continuous infusion. Ampules of 7.5 mg of glycopyrolate were added to 200 mL of saline and this infusion was titrated to the desired effects of dry mucous membranes and heart rate above 60 beats/min. During this study, atropine was used as a bolus for a heart rate less than 60 beats/min. The other apparent advantage to this regimen was a decreased number of respiratory infections. This may represent an alternative when there is a concern for respiratory infection due to excessive and difficult to control secretions, and in the presence of altered level of consciousness where the distinction between atropine toxicity or relapse of organophosphate poisoning is unclear.[27]

4. Pralidoxime. Before administration of pralidoxime, draw a blood sample (heparinized) for cholinesterase analysis (since pralidoxime tends to reverse the cholinesterase depression). Administer pralidoxime (Protopam, 2-PAM) a cholinesterase reactivator, in cases of severe poisoning by organophosphate pesticides in which respiratory depression, muscle weakness, and/or twitching are severe. (See dosage table on page 43.) When administered early (usually less than 48 hours after poisoning), pralidoxime relieves the nicotinic as well as the muscarinic effects of poisoning. Pralidoxime works by reactivating the cholinesterase and also by slowing the "aging" process of phosphorylated cholinesterase to a non-reactivatable form.

Note: Pralidoxime is of limited value and may actually be hazardous in poisonings by the cholinesterase-inhibiting carbamate compounds (see Chapter 5).

Dosage of Atropine:

In ***moderately severe poisoning*** (hypersecretion and other end-organ manifestations without central nervous system depression), the following dosage schedules have been used:

- *Adults and children over 12 years:* 2.0-4.0 mg, repeated every 15 minutes until pulmonary secretions are controlled, which may be accompanied by other signs of atropinization, including flushing, dry mouth, dilated pupils, and tachycardia (pulse of 140 per minute). **Warning:** In cases of ingestion of liquid concentrates of organophosphate pesticides, hydrocarbon aspiration may complicate these poisonings. Pulmonary edema and poor oxygenation in these cases will not respond to atropine and should be treated as a case of acute respiratory distress syndrome.
- *Children under 12 years:* 0.05-0.1 mg/kg body weight, repeated every 15 minutes until atropinization is achieved. There is a minimum dose of 0.1 mg in children. Maintain atropinization by repeated doses based on recurrence of symptoms for 2-12 hours or longer depending on severity of poisoning.

Maintain atropinization with repeated dosing as indicated by clinical status. Crackles in the lung bases nearly always indicate inadequate atropinization. Pulmonary improvement may not parallel other signs of atropinization. Continuation of, or return of, cholinergic signs indicates the need for more atropine. When symptoms are stable for as much as six hours, the dosing may be decreased.

Severely poisoned individuals may exhibit remarkable tolerance to atropine; two or more times the dosages suggested above may be needed. The dose of atropine may be increased and the dosing interval decreased as needed to control symptoms. Continuous intravenous infusion of atropine may be necessary when atropine requirements are massive. **The desired end-point is the reversal of muscarinic symptoms and signs with improvement in pulmonary status and oxygenation,** without an arbitrary dose limit. Preservative-free atropine products should be used whenever possible.

Note: Persons not poisoned or only slightly poisoned by organophosphates may develop signs of atropine toxicity from such large doses. Fever, muscle fibrillations, and delirium are the main signs of atropine toxicity. If these appear while the patient is fully atropinized, atropine administration should be discontinued, at least temporarily, while the severity of poisoning is reevaluated.

Dosage of Pralidoxime:

- *Adults and children over 12 years:* 1.0-2.0 g by intravenous infusion at a rate of no more than 0.2 g per minute. Slow administration of pralidoxime is strongly recommended and may be achieved by administering the total dose in 100 mL of normal saline over 30 minutes, or longer.
- *Children under 12 years:* 20-50 mg/kg body weight (depending on severity of poisoning) intravenously, mixed in 100 mL of normal saline and infused over 30 minutes.

Dosage of pralidoxime may be repeated in 1-2 hours, then at 10-12 hour intervals if needed. In very severe poisonings, dosage rates may be doubled. Repeated doses of pralidoxime are usually required. In cases that involve continuing absorption of organophosphate (as after ingestion of large amount), or continuing transfer of highly lipophilic organophosphate from fat into blood, it may be necessary to continue administration of pralidoxime for several days beyond the 48 hour post-exposure interval usually cited as the limit of its effectiveness. Pralidoxime may also be given as a continuous infusion of approximately 500 mg/hour based on animal case studies and adult patient reports.[28,29]

Blood pressure should be monitored during administration because of the occasional occurrence of hypertensive crisis. Administration should be slowed or stopped if blood pressure rises to hazardous levels. Be prepared to assist pulmonary ventilation mechanically if respiration is depressed during or after pralidoxime administration. If intravenous injection is not possible, pralidoxime may be given by deep intramuscular injection.

5. Skin decontamination. In patients who have been poisoned by organophosphate contamination of skin, clothing, hair, and/or eyes, decontamination must proceed concurrently with whatever resuscitative and antidotal measures are necessary to preserve life. Flush the chemical from the eyes with copious amounts of clean water. If no symptoms are evident in a patient who remains alert and physically stable, a prompt shower and shampoo may be appropriate, provided the patient is carefully observed to insure against any sudden appearance of poisoning. If there are any indications of weakness, ataxia, or other neurologic impairment, clothing should be removed and a complete bath and shampoo given while the victim is recumbent, using copious amounts of soap and water. Attendants should wear rubber gloves as vinyl provides no protection against skin absorption. Surgical green soap is excellent for this purpose, but ordinary soap is about as good. Wash the chemical from skin folds and from under fingernails.

Contaminated clothing should be promptly removed, bagged, and laundered before returning. Contaminated leather shoes should be discarded. Note that the pesticide can contaminate the inside surfaces of gloves, boots, and headgear.

6. Gastrointestinal decontamination. If organophosphate has been ingested in quantity probably sufficient to cause poisoning, consideration should be given to gastrointestinal decontamination, as outlined in Chapter 2, General Principles. If the patient has already vomited, which is most likely in serious exposures, further efforts at GI decontamination may not be indicated. In significant ingestions, diarrhea and/or vomiting are so constant that charcoal adsorption and catharsis are not indicated.

7. Observation. Observe patient closely for at least 72 hours to ensure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress, and sometimes pulmonary edema) do not recur as atropinization is withdrawn. In very severe poisonings by ingested organophosphates, particularly the more lipophilic and slowly hydrolyzed compounds, metabolic disposition of toxicant may require as many as 5-14 days. In some cases, this slow elimination may combine with profound cholinesterase inhibition to require atropinization for several days or even weeks. As dosage is reduced, the lung bases should be checked frequently for crackles. If crackles are heard, or if there is a return of miosis, bradycardia, sweating, or other cholinergic signs, atropinization must be re-established promptly.

8. Furosemide may be considered if pulmonary edema persists in the lungs even after full atropinization. It should not be used until the maximum benefit of atropine has been realized. Consult package insert for dosage and administration.

9. Pulmonary ventilation. Particularly in poisonings by large ingested doses of organophosphate, monitor pulmonary ventilation carefully, even after recovery from muscarinic symptomatology, to forestall respiratory failure. In some cases, respiratory failure has developed several days following organophosphate ingestion, and has persisted for days to weeks.

10. Hydrocarbon aspiration may complicate poisonings that involve ingestion of liquid concentrates of organophosphate pesticides. Pulmonary edema and poor oxygenation in these cases will not respond to atropine and should be treated as a case of acute respiratory distress syndrome.

11. Cardiopulmonary monitoring. In severely poisoned patients, monitor cardiac status by continuous ECG recording. Some organophosphates have significant cardiac toxicity.

12. Seizure control. Rarely, in severe organophosphate poisonings, convulsions occur despite therapy with atropine and pralidoxime. Insure that causes unrelated to pesticide toxicity are not responsible: head trauma, cerebral anoxia, or mixed poisoning. Drugs useful in controlling convulsions are discussed in Chapter 2. The benzodiazepines (diazepam or lorazepam) are the agents of choice as initial therapy.

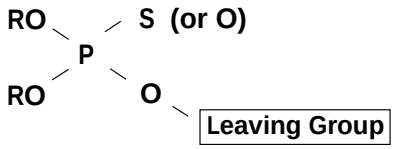
13. Contraindications. The following drugs are contraindicated in nearly all organophosphate poisoning cases: morphine, succinylcholine, theophylline, phenothiazines, and reserpine. Adrenergic amines should be given only if there is a specific indication, such as marked hypotension.

14. Re-exposures. Persons who have been clinically poisoned by organophosphate pesticides should not be re-exposed to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely and blood cholinesterase activities have returned to at least 80 percent of pre-poisoning levels. If blood cholinesterase was not measured prior to poisoning, blood enzyme activities should reach at least minimum normal levels (see table on page 39) before the patient is returned to a pesticide-contaminated environment.

15. Do not administer atropine or pralidoxime prophylactically to workers exposed to organophosphate pesticides. Prophylactic dosage with either atropine or pralidoxime may mask early signs and symptoms of organophosphate poisoning and thus allow the worker to continue exposure and possibly progress to more severe poisoning. Atropine itself may enhance the health hazards of the agricultural work setting: impaired heat loss due to reduced sweating and impaired ability to operate mechanical equipment due to blurred vision. This can be caused by mydriasis, one of the effects of atropine.

General Chemical Structure

R is usually either ethyl or methyl. The insecticides with a double bonded sulfur are organothiophosphates, but are converted to organophosphates in the liver. Phosphonate contains an alkyl (R-) in place of one alkoxy group (RO-). "X" is called the "leaving group" and is the principal metabolite for a specific identification.



References

1. DuBois KP. The toxicity of organophosphorous compounds to mammals. *Bull World Health Organ* 1971;44:233-40.
2. Pasquet J, Mazuret A, Fournel J, et al. Acute oral and percutaneous toxicity of phosalone in the rat, in comparison with azinphosmethyl and parathion. *Toxicol Appl Pharmacol* 1976;37:85-92.
3. Garcia-Repetto R, Martinez D, and Repetto M. Coefficient of distribution of some organophosphorus pesticides in rat tissue. *Vet Hum Toxicol* 1995;37:226-9.
4. Gallo MA and Lawryk NJ. Organic phosphorus pesticides. In: Haves WJ and Laws ER (eds), Handbook of Pesticide Toxicology, vol 2, Classes of Pesticides. San Diego, CA: Academic Press Inc., 1991.
5. Taylor P. Anticholinesterase agents. In: Gilman AG and Goodman LS (eds), The Pharmacological Basis of Therapeutics. New York: Macmillan Publishing Co. Inc.; 1985, pp.110-28.
6. De Kort WL, Kiestra SH, and Sangster B. The use of atropine and oximes in organophosphate intoxications: A modified approach. *Clin Toxicol* 1988;26:199-208.
7. Jamal JA. Neurological syndromes of organophosphorus compounds. *Adverse Drug React Toxicol Rev* 1997;16(3):133-70.
8. Steenland K, Jenkins B, Ames RG, et al. Chronic neurological sequelae to organophosphate poisoning. *Am J Public Health* 1994;84:731-6.
9. Savage E, Keefe T, Mounce L, et al. Chronic neurological sequelae of acute organophosphate pesticide poisoning. *Arch Environ Health* 1988;43:38-45.
10. Rosenstock L, Keifer M, Daniell W, et al. Chronic central nervous system effects of acute organophosphate pesticide intoxication. *Lancet* 1991;338:223-7.
11. Gershon S and Shaw FH. Psychiatric sequelae of chronic exposure to organophosphorus insecticides. *Lancet* 1961; 1:1371-4.
12. Metcalf DR and Holmes JH. EEG, psychological, and neurological alterations in humans with organophosphorus exposure. *Ann NY Acad Sci* 1969;160:357-65.
13. Holmes JH and Gaon MD. Observations on acute and multiple exposure to anticholinesterase agents. *Trans Am Clin Climatol Assoc* 1957; 68:86-103.
14. Hirshberg A and Lerman Y. Clinical problems in organophosphate insecticide poisoning: The use of a computerized information system. *Fundam Appl Toxicol* 1984; 4:S209-14.
15. Miller CS and Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. *Arch Environ Health* 1995; 50:119-29.
16. DeBleeker J, Willems J, Van Den Neucker K, et al. Prolonged toxicity with intermediate syndrome after combined parathion and methyl parathion poisoning. *Clin Toxicol* 1992;30:333-45.
17. DeBleecker J, Van Den Neucker K, and Colardyn F. Intermediate syndrome in organophosphorous poisoning: A prospective study. *Crit Care Med* 1993;21:1706-11.
18. Aldridge WN and Nemery B. Toxicology of trialkylphosphorothioates with particular reference to lung toxicity. *Fundam Appl Toxicol* 1984; 4:S215-23.
19. Bardin PG, Van Eeden SF, Moolman JA, et al. Organophosphate and carbamate poisoning. *Arch Intern Med* 1994;154:1433-41.
20. Zwiener RJ and Ginsburg CM. Organophosphate and carbamate poisoning in infants and children. *Pediatrics* 1988;81:121-683.
21. Sofer S, Tal A, and Shahak E. Carbamate and organophosphate poisoning in early childhood. *Pediatr Emerg Care* 1989;5(4):222-5.

22. Sullivan JB and Blose J. Organophosphate and carbamate insecticides. In: Sullivan JB and Krieger GR (eds), Hazardous Materials Toxicology. Baltimore, MD: Williams and Wilkins, 1992, pp. 1015-26.
23. Goswamy R, Chaudhuri A, and Mahashur AA. Study of respiratory failure in organophosphate and carbamate poisoning. *Heart Lung* 1994;23:466-72.
24. LeBlanc FN, Benson BE, and Gilg AD. A severe organophosphate poisoning requiring the use of an atropine drip. *Clin Toxicol* 1986;24:69-76.
25. DuToit PW, Muller FO, Van Tonder WM, et al. Experience with the intensive care management of organophosphate insecticide poisoning. *S Afr Med J* 1981;60:227-9.
26. Shockley LW. The use of inhaled nebulized atropine for the treatment of malathion poisoning. *Clin Toxicol* 1989;27:183-92.
27. Bardin PG and van Eeden SF. Organophosphate poisoning: Grading the severity and comparing treatment between atropine and glycopyrrolate. *Crit Care Med* 1990;18:956-60.
28. Thompson DF, Thompson GD, Greenwood RB, et al. Therapeutic dosing of pralidoxime chloride. *Drug Intell Clin Pharm* 1987;21:590-2.
29. Tush GM and Anstead MI. Pralidoxime continuous infusion in the treatment of organophosphate poisoning. *Ann Pharmacother* 1997;31:441-4.