CHAPTER 5

# Organophosphate Insecticides

Organophosphates (OPs) are a class of insecticides, several of which are highly toxic. Until the 21st century, they were among the most widely used insecticides available. Thirty-six of them are presently registered for use in the United States, and all can potentially cause acute and subacute toxicity. Organophosphates are used in agriculture, homes, gardens and veterinary practices; however, in the past decade, several notable OPs have been discontinued for use, including **parathion**, which is no longer registered for any use, and **chlorpyrifos**, which is no longer registered for home use. All share a common mechanism of cholinesterase inhibition and can cause similar symptoms, although there are some differences within the class. Since they share this mechanism, exposure to the same organophosphate by multiple routes or to multiple organophosphates by multiple routes may 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 dermal absorption, making specific identification of the agent and individualized management quite important.

## Toxicology

**Organophosphates** poison insects and other animals, including birds, amphibians 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, secretory cells and autonomic ganglia, and within the central nervous system (CNS). Once a critical proportion of the tissue enzyme mass is inactivated by phosphorylation, symptoms and signs of cholinergic 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 secretory 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. Impairment of the diaphragm and thoracic skeletal muscles can cause respiratory paralysis. 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 critical tissues.

Organophosphates are efficiently absorbed by inhalation and ingestion. Dermal penetration and subsequent systemic absorption varies with the specific agents. 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 1,500 mg/kg and 120 mg/kg, respectively.[2] In general, the highly toxic agents are more likely to have higher-order dermal toxicity

## COMMERCIAL PRODUCTS

*Highly Toxic[1]*

azinphos-methyl (Guthion, Gusathion)

bomyl[2] (Swat)

carbophenothion (Trithion)

chlorfenvinphos (Apachlor, Birlane)

chlormephos[2] (Dotan)

chlorthiophos[2] (Celathion)

coumaphos (Co-Ral, Asuntol)

cyanofenphos[2] (Surecide)

demeton[3] (Syntox)

dialifor (Torak)

dicrotophos (Bidrin)

dimefos[2] (Hanane, Pestox XIV)

dioxathion (Delnav)

disulfoton[3] (Disyston)

endothion[2]

EPN

ethyl parathion (E605, Parathion, thiophos)

famphur[2] (Famfos, Bo-Ana, Bash)

fenamiphos (Nemacur)

fenophosphon[2] (trichloronate, Agritox)

[1]*Compounds are listed approximately in order of descending toxicity. "Highly toxic" organophosphates have listed oral LD50 values (rat) less than 50 mg/kg; "moderately toxic" agents have LD50 values in excess of 50 mg/kg and less than 500 mg/kg.*

[2]*Products no longer registered in the United States.*

[3]*These organophosphates are systemic: they are taken up by the plant and translocated into foliage and sometimes into the fruit.*

than the moderately toxic agents. To a degree, the occurrence of poisoning depends on the rate at which the pesticide is absorbed. Breakdown occurs chiefly by hydrolysis in the liver, and rates of hydrolysis vary widely from one compound to another. In those organophosphates for which breakdown is relatively slow, significant temporary storage in body fat may occur. Some organophosphates, such as **diazinon**, **fenthion** and **methyl parathion**, have significant lipid solubility, allowing fat storage with delayed toxicity due to late release.[3,4] Delayed toxicity may also occur atypically with other organophosphates, specifically **dichlorofenthion** and **demton-methyl**.[5] 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 microsomal enzymes. Oxons are much more toxic than thions, but oxons break down more readily than thions. 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.

After the initial exposure of the effector junction and the organophosphate, the enzyme-phosphoryl bond is strengthened by loss of one alkyl group from the phosphoryl adduct. This process is known as aging. The bond is then essentially permanent. Time of aging varies by agent and can occur within minutes to days. Depending on the time of aging of the agent, some phosphorylated acetylcholinesterase enzyme can be de-phosphorylated (reactivated) by a compound known as an oxime. The only currently FDA-approved oxime in the United States is pralidoxime. Other oximes include obidoxime and HI-6, which have been used in Europe and Asia. Depending on the agent, pralidoxime reactivation may be no longer possible after a couple of days,[6] although in some cases, improvement has still been seen with pralidoxime administration days after exposure.[7] Oximes have been used for OP poisoning for more than 50 years.[8] However, controversy remains as to the effectiveness of oximes because of conflicting and limited evidence of efficacy.[4,9,10]

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). 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.[3,4,11] This delayed syndrome has been termed organophosphate-induced delayed neuropathy (OPIDN) and is manifested chiefly by weakness or paralysis and paresthesia of the extremities.[12] OPIDN predominantly affects the legs and may persist for weeks 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 that are candidate pesticides be tested in susceptible animal species for this neurotoxic property.

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 symptoms 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.[13,14] The most common compounds involved in this syndrome are methyl parathion, fenthion and **dimethoate**, although one case with **ethyl-parathion** was also observed.[4,13]

Other specific properties of individual organophosphates may render them more hazardous than basic toxicity data suggest. 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. *In vitro* and animal studies have demonstrated potentiation or additive effects when two or more organophosphates are absorbed simultaneously, thereby creating a cumulative effect.[15,16] Animal studies have also demonstrated additive effects when orgranophosphates are combined with other pesticides including herbicides, carbamates and pyrethroids.[17,18,19] Animal studies have demonstrated a protective effect of toxicity from phenobarbital, which induces hepatic degradation of the pesticide.[1] Degradation of some compounds to a trimethyl phosphate can cause restrictive lung disease.[20]

In the late 1950s and 1960s, several reports appeared suggesting that long-term effects have occurred following acute and often massive exposures. Symptoms that are consistently reported from exposed persons include depression, memory and concentration problems, irritability, persistent headaches and motor weakness.[21,22,23] In these rare, anecdotal cases, symptoms have persisted for months to years. These hypothesis-generating cases eventually led to larger epidemiological studies with an exposed group and a control group that also supported the hypothesis that a proportion of patients acutely poisoned from any organophosphate can experience some long-term neuropsychiatric sequelae. The findings included significantly impaired performance on a battery of neuro-behavioral tests and compound-specific peripheral neuropathy, in some cases. Specific functions included impaired memory and concentration, depressed mood and peripheral neuropathy. These findings were subtle and, in some cases, picked up only on neuropsychologic testing rather than during neurologic exam.[24,25,26] For information on chronic and long-term effects from OPs, including subacute effects and long-term exposure without acute poisoning, see **Chapter 21, Chronic Effects**.

## Signs and Symptoms of Poisoning

Symptoms of acute organophosphate poisoning develop during or after exposure, within minutes to hours, depending on method of exposure. Exposure by inhalation results in the fastest appearance of toxic symptoms, followed by the oral route and finally the dermal route. All signs and symptoms are cholinergic in nature and affect muscarinic, nicotinic and central nervous system receptors.[6] The critical symptoms in initial management are the respiratory symptoms. Sufficient muscular fasciculations and weakness are often observed and require respiratory support, as respiratory arrest can occur suddenly. Bronchospasm and bronchorrhea can occur, producing chest tightness, wheezing, productive cough and pulmonary edema. These can impede efforts at adequate oxygenation of the patient. A life-threatening severity of poisoning is signified by loss of consciousness, incontinence, seizures and respiratory depression. The primary cause of death is respiratory failure.

There usually is a secondary cardiovascular component to the respiratory symptoms. 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.[27] Toxic cardiomyopathy has been reported after severe poisoning due to sarin, a weaponized organophosphate compound structurally similar to the insecticides.[28]

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.

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Miosis is often a helpful diagnostic sign, and the patient may report blurred and/or dark vision. Anxiety and restlessness are prominent. There are a few reports of choreiform movements.[29,30] 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 often present with a slightly different clinical picture from adults. Four series have been published that describe children with poisoning from cholinesterase-inhibiting insecticides. Some of the more typical cholinergic signs of bradycardia, muscular fasciculations, lacrimation and sweating were less common. Seizures (range 8%-39%) and mental status changes, including lethargy and coma (range 55%-100%) were common in children.[31,32,33,34] In comparison, only around 2%-3% of adults present with seizures.[35,36] Other common presenting signs in children include flaccid muscle weakness, miosis and excessive salivation. In one of the studies, 80% of all cases were transferred with the wrong preliminary diagnosis.[33] In another study, 88% of parents initially denied a history of organophosphate exposure.[32] See the preceding section for information regarding the features of the intermediate syndrome and OPIDN.

## Confirmation of Poisoning

*CAUTION: **If strong clinical indications of acute organophosphate poisoning are present, treat patient immediately. Do not wait for laboratory confirmation, which can take days. Initial medical care should be based on clinical presentations.***

Blood samples can measure plasma butyrylcholinesterase (pseudocholinesterase) and red blood cell (RBC) AChE levels.[37] Depressions of plasma pseudocholinesterase and/or RBC acetylcholinersterase enzyme activities are generally available biochemical indicators of excessive organophosphate absorption. Rarely, there have been reports of cases of symptomatic organophosphate toxicity in which the initial red blood cell cholinesterase levels were not depressed. Subsequent testing eventually demonstrated depressed cholinesterase levels. Certain organophosphates may selectively inhibit either plasma pseudocholinesterase or RBC acetylcholinesterase.[38] 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. A 20%-30% depression of AChE may indicate a significant OP poisoning that, even without symptoms, needs antidotal treatment. In severe cases, the enzyme is usually depressed by 80%-90% of normal levels. The latter group typically requires significantly high doses of atropine.[4,37] 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. Lower limits of cholinesterase levels vary among laboratories and methods, so clinicians should interpret levels based on the given reference ranges. Patients with clinical signs of toxicity and accompanied by AChE levels depressed by 20%-50% should be managed as outlined in the treatment section.

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 succinylcho-

line, often administered to surgical patients, but not 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, oral contraception 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 reduced, however, 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. These metabolites are among the numerous chemical metabolites measured in a U.S. sample via the National Health and Nutrition Education Survey (NHANES) and can be found in CDC's National Report on Human Exposure to Environmental Chemicals.[39]

Detection of intact organophosphates in the blood usually is not possible except during or soon after absorption of a substantial amount. In general, organophosphates do not remain unhydrolyzed in the blood more than a few minutes or hours, unless the quantity absorbed is large or the hydrolyzing liver enzymes are inhibited. Blood should be obtained for cholinesterase testing as described above, but it is not feasible or practical to attempt to test for specific compounds. It may be useful to obtain a urine sample from the poisoned patient and send it for metabolite detection as discussed in the preceding paragraph. For a patient with an unknown poisoning, a frozen sample of urine for later testing may be useful.

## Treatment of Organophosphate Toxicosis

*CAUTION: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. All caregivers should have appropriate protective gear when in contact with a patient poisoned by organophosphates. Wear rubber gloves while washing pesticide from skin and hair.*

1. 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 and keep patient on a high $FiO_2$. In severe poisonings, patients should be treated in an intensive care unit setting.

2. 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 or more may be required,[40] or even continuous infusion.[41, 42] (See dosage on following page.)

*Moderately Toxic*
*Commercial Products*
*continued*

malathion (Cythion)

merphos (Folex, Easy Off-D)

methyl trithion[2], dimethoate (Cygon, DeFend)

naled (Dibrom)

oxydemeton-methyl[3] (Metasystox-R)

oxydeprofos[2,3] (Metasystox-S)

phencapton[2] (G 28029)

phenthoate[2] (dimephenthoate, Phenthoate)

phosalone (Zolone)

phosmet (Imidan, Prolate)

phoxim[2] (Baythion)

pirimiphos-ethyl[2] (Primicid)

pirimiphos-methyl (Actellic)

profenofos (Curacron)

propetamphos (Safrotin)

propyl thiopyrophosphate[2] (Aspon)

pyrazophos[2] (Afugan, Curamil)

pyridaphenthion[2] (Ofunack)

quinalphos[2] (Bayrusil)

ronnel (Fenchlorphos, Korlan)

sulprofos[2] (Bolstar, Helothion)

temephos (Abate, Abathion).

tetrachlorvinphos (Gardona, Apex, Stirofos)

thiometon[2] (Ekatin)

triazophos[2] (Hostathion)

trichlorfon (Dylox, Dipterex, Proxol, Neguvon)

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, and multiple doses will be required. 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 can help differentiate poisoning by anticholinesterase agents from other conditions.

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### Test Dosage of Atropine

- *Adults: 1 mg*
- *Children under 12 years: 0.01 mg/kg*

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Note, however, that lack of response with no evidence of atropinization (atropine refractoriness), may also indicate a more severe poisoning. The adjunctive use of nebulized atropine has been reported to improve respiratory distress, decrease bronchial secretions and increase oxygenation.[43]

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### 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: Initial dose 1-3 mg IV. Repeat in 3-5 minutes if no change in clinical symptoms. Dose may be doubled with each administration until the patient is atropinized. Once adequate atropinization has been achieved, the patient can be maintained on an atropine continuous infusion at about 10%-20% of the loading dose and titrated to effect.[4,44,45,46]*

- *Children under 12 years: There is less agreement regarding pediatric dosing. Recent studies recommend beginning with 0.02 mg/kg body weight, and doubling the dose every 5 minutes until atropinization is achieved.[4,44] Patients seen in a pediatric ICU setting were given 0.05 mg/kg every 15 minutes.[31] Since children sometimes present differently than adults and have more CNS findings, aggressive atropinization should proceed when there are muscarinic signs such as bradycardia, salivation, diarrhea and miosis that can be observed to change with adequate atropine.[31]*

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Clear breath sounds and absent pulmonary secretions are the primary end-point. Other signs of atropinization may occur, including flushing, dry mouth, dilated pupils and tachycardia (pulse of 140 per minute). Early in therapy, monitor for improving blood pressure and heart rate (above 80 beats/minute), normal pupil size and drying of the skin and axillae.[4,45]

*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.*

Maintain atropinization by repeated doses based on recurrence of symptoms for 2–12 hours or longer depending on severity of poisoning. Crackles in the lung bases usually 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.

Maintain atropinization with repeated dosing as indicated by clinical status. When symptoms are stable for as much as 6 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, most predominantly drying of secretions, and signs of 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 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.*

3. Consider administering glycopyrrolate. Glycopyrrolate has been studied as an alternative to atropine and found to have similar outcomes using continuous infusion. Ampules of 7.5 mg of glycopyrrolate were added to 200 mL of saline, and this infusion was titrated to the desired effects of dry mucous membranes, heart rate above 60 beats/minute and absent muscle fasciculations. During this study, atropine was used as a bolus for a heart rate less than 60 beats/minute. 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 distinction between atropine toxicity or relapse of organophosphate poisoning is unclear.[47]

4. Draw a blood sample (heparinized) for cholinesterase analysis before administration of pralidoxime, which tends to reverse the cholinesterase depression.

5. Consider administering pralidoxime (Protopam, 2-PAM), a cholinesterase reactivator, in cases of moderate-to-severe OP poisoning in which respiratory depression, muscle weakness and/or twitching are severe. Pralidoxime works by reacti-

vating the cholinesterase and also by slowing the "aging" process, in which there is a loss of an akyl group. The AChE can no longer be reactivated. It is important to administer it early in the poisoning, preferably within 48 hours; however, this varies by the OP that is ingested. Some OPs will age much faster than others, (*e.g.,* parathion ages within 20 minutes, while diethyl-OPs tend to require >48 hours). Pralidoxime given after the aging process will be ineffective. Delayed treatment appears to be one factor in previous studies with oximes and OP poisoning that did not show a beneficial effect. [48,49]

As noted previously, there are limited data supporting the efficacy of oximes in OP poisoning, particularly from randomized controlled trials (RCTs), although they have been used for over 50 years.[37,50,51] One recent RCT demonstrated that pralidoxime substantially and moderately reactivated red cell AChE activity in patients poisoned by diethyl and dimethyl compounds, respectively, when given as a continuous infusion of 500 mg/hour. Though mortality was higher in the group receiving pralidoxime, the difference was not statistically significant.[9]

Another well-designed RCT compared two different dosing regimens after all patients first received a 2-gram loading dose of pralidoxime. The authors found that a continuous infusion of 1 gram of pralidoxime per hour was superior to what had been previously considered a standard bolus dosing of 1 gram pralidoxime every 4 hours. Mortality and morbidity, as measured by atropine requirements, need for intubation and duration of ventilator support, were all reduced in the group receiving continuous infusion. In this study, both groups appear to have received appropriate intensive care management that would closely match care provided in a U.S. hospital.[10] While further study is needed, particularly as to optimal dose and delivery time with respect to type of OP ingested, pralidoxime continues to be recommended in the United States for moderate-to-severe OP poisoning. Unfortunately, all studies have been performed on adults, so there are no adequate or updated data regarding proper dosing for children.

**NOTE:** *Pralidoxime is of limited value, and may be hazardous, in poisonings by the cholinesterase-inhibiting carbamate compounds (see* **Chapter 6***).*

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### Dosage of Pralidoxime

**Loading Dose**

• *Adults and children over 12 years: 2.0 gm by intravenous infusion over a 30-minute period.[10]*

• *Children under 12 years: 20-50 mg/kg body weight given intravenously (depending on severity of poisoning), mixed in 100 mL of normal saline and infused over 30 minutes.*

**Subsequent Dose**

• *1 gram per hour as a continuous infusion over a 48-hour period. Subsequent doses, if required, should be given every 4 hours, infused over an hour. Alternatively, dosage of pralidoxime may be repeated in 1-2 hours, then at 4-hour intervals if needed.*

Repeated doses of pralidoxime are usually required. Dosing should continue while ventilator support is 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.

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, the bolus regimen of pralidoxime may be given by deep intramuscular injection.

6. Decontaminate skin, clothing, hair and/or eyes of patients who have been poisoned by organophosphates, concurrently with whatever resuscitative and antidotal measures are necessary to preserve life. Decontaminate eyes by flushing 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 ensure against sudden appearance of poisoning symptoms. If there are any indications of weakness, ataxia or other neurologic impairment, clothing should be removed and a complete bath and shampoo, using copious amounts of soap and water, should be given while the victim is recumbent. Attendants should wear rubber gloves, as latex or polyvinyl chloride provides no protection against skin absorption.[52,53] Even nitrile butadiene rubber gloves exhibited some defects following exposure to chlorpyrifos and diazinon, although these appeared much later (24-48 hours after exposure) compared to some almost immediate defects appearing in PVC gloves.[52] The possibility of pesticide sequestered under fingernails or in skin folds should not be overlooked. Contaminated clothing should be promptly bagged and not returned until it has been thoroughly laundered. Contaminated leather shoes should be discarded. Pesticide may have contaminated the inside surfaces of gloves, boots and/or headgear as well.

7. Consider gastrointestinal decontamination if organophosphate has been ingested in quantity sufficient to cause poisoning, if the patient receives care within 30 minutes of the exposure and if there is sufficient airway protection. 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.

   A. Take rigorous precautions to protect the airway from aspiration of regurgitated gastric contents. If a victim is unconscious, obtunded, has an altered mental status or any respiratory compromise, orotracheal intubation should be performed prior to gastric aspiration.

   B. Save a sample of emesis or initial gastric aspirate for chemical analysis.

8. Observe patient closely for at least 72 hours after atropinization has been withdrawn to ensure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress, and sometimes pulmonary edema) do not recur. In very severe poisonings by ingested organophosphates, particularly the more lipophilic and slowly hydrolyzed compounds, metabolic disposition of toxi-

cant 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 reestablished promptly.

9. Monitor pulmonary status carefully even after apparent recovery from muscarinic symptoms, particularly in poisonings by large ingested doses of organophosphate. In some cases, respiratory failure has developed several days following organo-phosphate ingestion, and has persisted for days to weeks.

10. Monitor cardiac status in severely poisoned patients by continuous ECG recording. Some organophosphates have significant cardiac toxicity.

11. Do not use the following drugs: morphine, succinylcholine, theophylline, pheno-thiazines and reserpine. They are contraindicated in nearly all organophosphate poisoning cases. Adrenergic amines should be given only if there is a specific indication, such as marked hypotension.

12. If seizures occur despite therapy with atropine and pralidoxime, ensure that causes unrelated to pesticide toxicity are not responsible: head trauma, cerebral anoxia or mixed poisoning. Seizures occur rarely in severe organophosphate poisonings. Drugs useful in controlling seizures are discussed in **Chapter 3,** *General Principles*. The benzodiazepines − diazepam or lorazepam − are the agents of choice as initial therapy.

13. Warn persons who have been clinically poisoned by organophosphate pesticides to avoid re-exposure to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely and blood cholinesterase activities have returned to at least 80% of pre-poisoning levels. If blood cholinesterase was not measured prior to poisoning, blood enzyme activities should reach at least minimum normal levels before the patient is returned to a pesticide-contaminated environment.

14. Treat ingestion of liquid concentrates of organophosphate pesticides like a case of acute respiratory distress syndrome. Hydrocarbon aspiration may complicate these poisonings. Pulmonary edema and poor oxygenation in these cases will not respond to atropine.

15. Do not administer atropine or pralidoxime prophylactically to workers exposed to organophosphate pesticides. Prophylactic dosage with either atropine or prali-doxime 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, impairing heat loss (due to reduced sweating) and impairing the ability to operate mechanical equipment (due to blurred vision caused by mydriasis).

## References

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