Organophosphate and carbamate poisoning

INTRODUCTION — Organophosphates and carbamates are potent cholinesterase inhibitors capable of causing severe cholinergic toxicity following cutaneous exposure, inhalation, or ingestion. Although structurally distinct [1], organophosphates and carbamates exhibit similar clinical manifestations with toxicity and require similar management following overdose.

An overview of organophosphate and carbamate poisoning will be presented here. A summary table to facilitate emergent management is provided (table 1). A general approach to suspected drug intoxication is discussed separately. (See "General approach to drug poisoning in adults".)

EPIDEMIOLOGY AND SOURCES OF EXPOSURE — Organophosphates have been used as insecticides worldwide for more than 50 years. The use of these agents has declined in the last 10 to 20 years, in part due to the development of carbamate insecticides, which are associated with similar toxicities [1]. Medical applications of organophosphates and carbamates include reversal of neuromuscular blockade (neostigmine, pyridostigmine, edrophonium) and treatment of glaucoma, myasthenia gravis, and Alzheimer disease (echothiophate, pyridostigmine, tacrine, and donepezil).

Worldwide, an estimated 3,000,000 people are exposed to organophosphate or carbamate agents each year, with up to 300,000 fatalities [2,3]. In the United States, there were more than 8000 reported exposures to these agents in 2008, resulting in fewer than 15 deaths [4]. Toxicity generally results from accidental or intentional ingestion of, or exposure to, agricultural pesticides [2,5]. Other potential causes of organophosphate or carbamate toxicity include ingestion of contaminated fruit, flour, or cooking oil, and wearing contaminated clothing [5,6].

Specific agents linked to human poisoning include both carbamate (methomyl and aldicarb) and organophosphate (parathion, fenthion, malathion, diazinon, and dursban) insecticides. Chlorpyrifos, the organophosphate agent of dursban, is found in some popular household roach and ant sprays, including Raid and Black Flag (figure 2). The United States Environmental Protection Agency (EPA) banned many household uses of chlorpyrifos in 2001, and has restricted its use on certain crops including tomatoes, apples, and grapes [7].

Several organophosphorus nerve agents (eg, tabun [GA], sarin [GB], soman [GD]) were developed in Germany during the 1940s, but were not used for military purposes [8]. The 1995 sarin attack on the Tokyo subway system by the religious cult Aum Shinrikyo and subsequent international events have heightened awareness regarding the prevention, recognition, and treatment of casualties due to organophosphorus ("nerve") agent exposure [9-11]. (See "Chemical terrorism: Rapid recognition and initial medical management".)

MECHANISM OF ACTION — Organophosphorus compounds contain carbon and phosphorous acid derivatives (figure 1). These agents are well absorbed through the skin, lungs, and gastrointestinal tract. They bind to acetylcholinesterase (AChE), also known as red blood cell (RBC) acetylcholinesterase, and render this enzyme non-functional. AChE is the enzyme responsible for hydrolysis of acetylcholine to choline and acetic acid, and inhibition leads to an overabundance of acetylcholine at the neuronal synapses and the neuromuscular junction [12,13].

After some period of time (dependent on the chemical structure of the organophosphorus agent), the acetylcholinesterase-organophosphorus compound undergoes a conformational change, known as "aging," which renders the enzyme irreversibly resistant to reactivation by an antidotal oxime (figure 3) [14].

In addition, plasma cholinesterase (also called butyrylcholinesterase [BuChE] or pseudocholinesterase) and neuropathy target esterase (NTE) are inhibited by organophosphorus agents; however, the clinical significance of these interactions is less certain [15,16].

Carbamate compounds are derived from carbamic acid (figure 1). Like organophosphorus agents, carbamates are
CLINICAL FEATURES — Onset and duration of AChE inhibition varies depending on the organophosphorus agent’s rate of AChE inhibition, the route of absorption, enzymatic conversion to active metabolites, and the lipophilicity of the organophosphorus agent. For most agents, oral or respiratory exposures generally result in signs or symptoms within three hours, while symptoms of toxicity from dermal absorption may be delayed up to 12 hours. Lipophilic agents such as dichlofenthion, fenthion, and malathion are associated with delayed onset of symptoms (up to five days) and prolonged illness (greater than 30 days), which may be related to rapid adipose fat uptake and delayed redistribution from the fat stores (table 1). The great variability in toxicity and treatment response among organophosphorus agents, however, is not well understood, leading some to suggest that each agent be considered independently in future studies [17].

Acute toxicity

Cholinergic excess — Acute toxicity from organophosphorus agents presents with manifestations of cholinergic excess. Primary toxic effects involve the autonomic nervous system, neuromuscular junction, and central nervous system (CNS) [18]. The parasympathetic nervous system is particularly dependent on acetylcholine regulation, since both the autonomic ganglia and end organs of the parasympathetic nervous system are regulated by nicotinic and muscarinic cholinergic receptor subtypes, respectively (figure 4).

The dominant clinical features of acute cholinergic toxicity include bradycardia, miosis, lacrimation, salivation, bronchorrhea, bronchospasm, urination, emesis, and diarrhea. Diaphoresis occurs because sweat glands are regulated through sympathetic activation of postganglionic muscarinic receptors. At times, however, mydriasis and tachycardia may be observed, as sympathetic ganglia also contain nicotinic receptors (figure 4).

The muscarinic signs can be remembered by use of one of two mnemonics:

- **SLUDGE/BBB** — Salivation, Lacrimation, Urination, Defecation, Gastric Emesis, Bronchorrhea, Bronchospasm, Bradycardia
- **DUMBELS** — Defecation, Urination, Miosis, Bronchorrhea/Bronchospasm/Bradycardia, Emesis, Lacrimation, Salivation [19]

It should be noted that these mnemonics do **NOT** take into account the critical CNS and nicotinic effects of these toxins. The nicotinic effects include fasciculations, muscle weakness, and paralysis via acetylcholine stimulation of receptors at the neuromuscular junction. This mechanism is analogous to the depolarizing effects of succinylcholine in producing neuromuscular blockade. Nicotinic and muscarinic receptors also have been identified in the brain, and may contribute to central respiratory depression, lethargy, seizures, and coma (figure 4).

Cardiac issues — Cardiac arrhythmias, including heart block and QTc prolongation, are occasionally observed in organophosphorus agent poisoning [20]. It is unclear whether these arrhythmias are due to direct toxicity or secondary hypoxemia.

Case reports and small case series suggest that up to one-third of patients with severe OP poisoning manifest signs of myocardial ischemia, such as an elevated troponin or changes in the electrocardiogram (ECG) [21,22]. Peak troponin concentrations occur at presentation in most cases. Risk appears to be greatest in older patients and those with severe poisoning, but low in patients with mild poisoning. (See "Electrocardiogram in the diagnosis of myocardial ischemia and infarction".)

Respiratory issues — Fatalities from acute organophosphorus agent poisoning generally result from respiratory failure due to a combination of depression of the CNS respiratory center, neuromuscular weakness, excessive respiratory secretions, and bronchoconstriction. Fatalities also occur due to cardiovascular collapse; although the mechanism of this dysfunction is not completely understood, inappropriate vasodilation may play a role [23].

Intermediate (neurologic) syndrome — Ten to 40 percent of patients poisoned with organophosphorus develop a distinct neurologic disorder 24 to 96 hours after exposure. This disorder, referred to as the "intermediate syndrome," consists of characteristic neurological findings including neck flexion weakness, decreased deep tendon reflexes, cranial nerve abnormalities, proximal muscle weakness, and respiratory insufficiency [24-26].

Risk factors for the development of intermediate syndrome appear to include exposure to a highly fat-soluble organophosphorus agent, and may be related to inadequate doses of oximes [27]. The intermediate syndrome has
blood cell (RBC) acetylcholinesterase levels. Nerve conduction studies on patients with intermediate syndrome reveal unique postsynaptic abnormalities that differentiate this disorder from delayed neurotoxicity (see "Delayed and long-term neuropathology" below) [28]. (See "Differential diagnosis of peripheral nerve and muscle disease".)

**Delayed and long-term neuropathology** — Organophosphorus agent induced delayed neuropathy (OPIDN) typically occurs one to three weeks after ingestion of one of a small number of specific organophosphorus agents, including chlorpyrifos (figure 5) [29,30]. Carbamates are only rarely associated with the development of OPIDN [31,32]. The mechanism may involve inhibition of neuropathy target esterase (NTE), rather than alterations in RBC acetylcholinesterase function (see 'Mechanism of action' above) [33]. This enzyme, which is found in the brain, peripheral nerves, and lymphocytes, is responsible for the metabolism of various esters within the cell.

Affected patients present with transient, painful "stocking-glove" paresthesias followed by a symmetrical motor polyneuropathy characterized by flaccid weakness of the lower extremities, which ascends to involve the upper extremities. Sensory disturbances are usually mild. Delayed neurotoxicity primarily affects distal muscle groups; severe neurotoxicity, proximal muscles groups may also be affected [34]. Electromyograms and nerve conduction studies of affected patients revealed decreased firing of motor conduction units [35]. Histopathologic sections of peripheral nerves reveal Wallerian (or "dying-back") degeneration of large distal axons [36]. (See "Differential diagnosis of peripheral nerve and muscle disease".)

The risk of developing OPIDN is independent of the severity of acute cholinergic toxicity. Some organophosphorus agents, such as parathion, are potent cholinergic agents but are not associated with OPIDN. Others, such as triorthocresyl phosphate (TOCP), produce few clinical signs of cholinergic excess but are frequently implicated in OPIDN (figure 5) [37]. Most cases of mild delayed neurotoxicity improve with time; in severe cases, an upper motor neuron syndrome with spasticity of the lower extremities usually causes permanent disability.

Survivors of acute organophosphorus agent poisoning may have neurobehavioral deficits such as decreased memory, abstraction, and Parkinsonism, which may be permanent [38]. It is unclear if these neurocognitive effects are due to direct neurotoxicity of organophosphorus agents themselves, or related to hypoxia and other non-specific effects of serious illness.

**Additional effects** — Several case reports describe acute kidney injury (AKI) requiring renal replacement therapy in the setting of severe organophosphate poisoning [39,40]. Causality has not been established and it remains unclear whether the AKI is due directly to the OP or the general effects of critical illness, but in severe OP poisoning it is prudent to monitor renal function. Acute pancreatitis may complicate poisoning caused by either organophosphates or carbamates [41].

**DIAGNOSIS**

**Clinical findings** — The diagnosis of organophosphate or carbamate poisoning is made on clinical grounds. In the absence of a known ingestion or exposure, the clinical features of cholinergic excess should indicate the possibility of organophosphate poisoning. Many organophosphorus agents have a characteristic petroleum or garlic-like odor, which may be helpful in establishing the diagnosis. (See "General approach to drug poisoning in adults".)

Due to significant variability in toxicity, every effort should be made to precisely identify the agent. It is imperative to determine if a dimethyl or a diethyl poison was involved (figure 1). The duration of toxicity and the therapeutic window during which oxime treatment is likely to be effective are markedly different for these two classes of toxins. Dimethyl compounds undergo rapid aging, making early initiation of oxime therapy critical; diethyl compounds may exhibit delayed toxicity, and may require prolonged treatment [3].

If doubt exists as to whether an organophosphate or carbamate has been ingested, a trial of 1 mg atropine in adults (or 0.01 to 0.02 mg/kg in children) may be employed. The absence of signs or symptoms of anticholinergic effects following atropine challenge strongly supports the diagnosis of poisoning with an acetylcholinesterase inhibitor.

**Laboratory abnormalities** — Direct measurement of RBC acetylcholinesterase (RBC AChE) activity provides a measure of the degree of toxicity. Sequential measurement of RBC AChE activity (if rapidly available) may also be used to determine the effectiveness of oxime therapy in regeneration of the enzyme. Determination of RBC AChE activity can also be helpful in evaluating chronic or occupational exposure. However, most hospital laboratories are unable to perform this test. An assay for plasma (or pseudo-) cholinesterase activity is more easily performed, but...
Initial resuscitation — Moderately to severely poisoned patients with markedly depressed mental status require 100 percent oxygen and immediate endotracheal intubation. In addition, patients who appear mildly poisoned may rapidly develop respiratory failure due to a combination of CNS respiratory center depression, nicotinic receptor mediated diaphragmatic weakness, bronchospasm, and copious secretions. Thus, patients with mild to moderate poisoning should also be considered for early endotracheal intubation. A summary table to facilitate emergent management is provided (table 1).

Clinicians should avoid the use of succinylcholine when performing rapid sequence intubation (RSI) in patients with organophosphate (OP) poisoning. Succinylcholine is metabolized by acetylcholinesterase (which is inhibited by OP compounds) leading to exaggerated and prolonged neuromuscular blockade in poisoned patients. Nondepolarizing neuromuscular blocking agents (eg, rocuronium) can be used, but may be less effective at standard doses due to competitive inhibition at the neuromuscular junction. Therefore, increased doses will likely be needed. (See "Definition, classification, etiology, and pathophysiology of shock in adults".)

Bradycardia and hypotension are usually present in moderate to severe poisonings. However, tachycardia or hypertension may transiently occur due to direct sympathetic stimulation. Adequate volume resuscitation with isotonic crystalloid (eg, normal saline or lactated Ringer's solution) should be performed concomitantly with other resuscitative and diagnostic efforts. (See "Definition, classification, etiology, and pathophysiology of shock in adults").

Cholinergic toxicity — Patients with cholinergic toxicity due to organophosphate or carbamate poisoning are treated with atropine and oxime therapy (typically pralidoxime) as described below.

Atropine — Atropine competes with acetylcholine at muscarinic receptors, preventing cholinergic activation. For moderate to severe cholinergic toxicity, atropine should be administered beginning at a dose of 2 to 5 mg IV for adults and 0.05 mg/kg IV for children. If no effect is noted, the dose should be doubled every three to five minutes until pulmonary muscarinic signs and symptoms are alleviated. It is not necessary to provide oxygen prior to initiating treatment with atropine [43].

Atropine dosing should be titrated to the therapeutic end point of the clearing of respiratory secretions and the cessation of bronchoconstriction [44]. Tachycardia and mydriasis are NOT appropriate markers for therapeutic improvement, as they may indicate continued hypoxia, hypovolemia, or sympathetic stimulation. In patients with severe poisoning, HUNDREDS of milligrams of atropine by bolus and continuous infusion may be required over the course of several days.

This individualized approach to treatment is supported by the results of an open label randomized trial in which patients (n = 156) treated with incremental doses of atropine plus infusion experienced lower mortality (6 versus 18 deaths) and fewer episodes of atropine toxicity than patients treated with a standard bolus dose plus infusion [45].

In June 2003, the United States Food and Drug Administration (FDA) approved pediatric doses of Atropen (atropine autoinjector) for children and adolescents exposed to certain nerve agents and pesticides [46]. Atropen is designed for acute use by nonphysicians trained in the recognition and treatment of nerve agent or insecticide intoxication. The approved doses for mild symptoms of nerve agent poisoning vary by weight, as follows:

- 15 to 40 pounds (7 to 18 kg): 0.5 mg
- >40 to 90 pounds (>19 to 41 kg): 1.0 mg
- >90 pounds and adults (>41 kg): 2.0

Up to three times these doses may be administered to children with acute symptoms of severe nerve agent poisoning.

Pralidoxime — Since atropine does not bind to nicotinic receptors, it is ineffective in treating neuromuscular dysfunction. Pralidoxime (2-PAM) and other oximes, such as HI-6 and obidoxime, are cholinesterase reactivating agents that are effective in treating both muscarinic and nicotinic symptoms (figure 3) [3,13,47]. Pralidoxime should NOT be administered without concurrent atropine in order to prevent worsening symptoms due to transient oxime-induced acetylcholinesterase inhibition [48].

We suggest that oxime therapy be given to all patients with evidence of cholinergic toxicity, patients with neuromuscular dysfunction, or patients with exposures to organophosphorous agents known to cause delayed neurotoxicity (figure 5). The current World Health Organization recommendation for IV bolus therapy with pralidoxime is http://www.uptodate.com/contents/organophosphate-and-carbamate-poisoning?topicKey=EM%2F339&elapsedTimeMs=5&source=search_result&searchTerm=carbamato&selectedTitle=1~37&view=print&displayedView=full.
Pralidoxime should be administered slowly over 30 minutes, since rapid administration has occasionally been associated with cardiac arrest, and slow administration prevents the muscle weakness that results from the transient inhibition of acetylcholinesterase as pralidoxime binds to the enzyme [51]. After the bolus dose, it appears that superior antidotal effects occur with pralidoxime given as a continuous infusion of at least 8 mg/kg per hour in adults and 10 to 20 mg/kg per hour for children [49,52].

Severe poisonings may result in prolonged redistribution of toxin; therefore, continuous IV therapy should be adjusted based upon the patient’s clinical response, and several days of therapy may be required [53]. If rapidly available, serial red blood cell acetylcholinesterase (RBC AChE) concentrations may be valuable in determining the efficacy of oxime-induced acetylcholinesterase regeneration.

Evidence about the use of oximes to treat OP poisoning is inconsistent and difficult to interpret [54]. There appears to be great variability among victims of organophosphorus poisoning in their clinical response to pralidoxime, which is not well understood. In one large, prospective study, patients poisoned with diethyl compounds (eg, chlorpyrifos) had significantly lower mortality and intubation rates following treatment with pralidoxime than those poisoned with dimethyl agents (eg, dimethoate, fenithion) [17]. Conversely, in a small, double-blinded randomized trial, no significant benefit, and a trend towards harm, was found in the group treated with pralidoxime compared to patients given placebo, regardless of the type of organophosphate ingested [55]. Until this variability is better understood and other treatments become available, we believe that all patients poisoned with organophosphorus agents should be treated with an oxime.

Seizures — Organophosphorus agent-induced seizures should be treated with a benzodiazepine. Prophylactic diazepam has been shown to decrease neurocognitive dysfunction after organophosphorus agent poisoning [56,57]. This led, in part, to the United States military development of a 10 mg autoinjector of diazepam for use in the setting of chemical attack [58,59]. There is no evidence that phenytoin has any effect on organophosphorus agent-induced seizures, and this agent is not recommended.

Decontamination — In cases of topical exposure with potential dermal absorption, aggressive decontamination with complete removal of the patient’s clothes and vigorous irrigation of the affected areas should be performed. The patient’s clothes and belongings should be discarded since they absorb organophosphorus agents, and reexposure may occur even after washing. Health care workers must take precautions to avoid accidental exposure, including providing treatment in a well-ventilated area [10,60,61]. (See "Chemical terrorism: Rapid recognition and initial medical management".)

We generally do not perform gastric lavage. Nevertheless, some clinicians may elect to do so in patients who present less than one hour following ingestion of an organophosphorus agent, AFTER performing endotracheal intubation and initiating therapy with atropine and an oxime. Gastric lavage involves substantial risk of aspiration in patients with increased secretions and decreased mental status, and this intervention has never been shown to decrease morbidity or mortality [44].

Following initial resuscitation and treatment, we suggest activated charcoal (AC) be given to patients presenting within one hour of an organophosphorus agent or carbamate ingestion. The standard dose is 1 g/kg (maximum dose 50 g). We do not give AC to patients presenting more than one hour following ingestion. Findings from randomized and observational trials suggest that AC given after the first hour provides no benefit to patients with these ingestions [62].

Forced emesis is contraindicated because of the risk of aspiration and seizures. Urinary alkalization has been suggested, but there is no clear evidence that this intervention improves outcome [63]. (See "Gastrointestinal decontamination of the poisoned patient" and "Enhanced elimination of poisons".)

Cardiac complications — Cardiac complications are typically not the major morbidity associated with OP poisoning, and management is best focused on treating cholinergic toxicity. Based on limited evidence, we believe it is reasonable to monitor patients with severe poisoning for myocardial ischemia by obtaining serial electrocardiograms and serum troponin concentrations approximately every 8 to 12 hours while the patient’s condition remains critical. Given that many of these cases are managed in resource-limited settings, the appropriate level of monitoring will vary.

In the setting of OP poisoning, myocardial ischemia appears to stem from non-occlusive disease. Treatment with aspirin is probably safe and prudent. We do not suggest other therapies. Should arrhythmias develop, we suggest standard treatments based on the protocols of Advanced Cardiac Life Support. Note that ventricular tachycardia is the...
PROGNOSIS — In the only prospective study to examine prognostic factors for patients acutely poisoned with OP or carbamate (n = 1365), the authors found that a Glasgow Coma Score (GCS) of less than 13 portends a poor prognosis, and using the GCS was as good as using the International Program on Chemical Safety Poison Severity Score (IPCS PSS) [64]. However, the authors point out that the OP agent involved must be taken into account, as one-half of the fenthion-poisoned patients who died had only mild symptoms at presentation. A retrospective study of nearly 400 OP-poisoned patients examined the performance of several standard ICU-based clinical scoring systems [65]. This study reported that the Acute Physiology and Chronic Health Evaluation II (APACHE-II), Simplified Acute Physiology Score II (SAPS-II), and the Mortality Prediction Model II (MPM-II) scoring systems outperformed the Poisoning Severity Scale in predicting death. Again, however, the performance of these scoring systems was partly dependent upon the OP agent involved.

Until larger prospective studies can be performed, we suggest using one of the above clinical scoring systems to help determine prognosis, but only for those specific OP-pesticides that were included in the relevant study. Particular attention must be given to patients poisoned with lipophilic OPs such as fenthion and parathion, as these patients may exhibit delayed and prolonged poisoning symptoms.

ADDITIONAL RESOURCES — Regional poison control centers in the United States are available at all times for consultation on patients who are critically ill, require admission, or have clinical pictures that are unclear (1-800-222-1222). In addition, some hospitals have clinical and/or medical toxicologists available for bedside consultation and/or inpatient care. Whenever available, these are invaluable resources to help in the diagnosis and management of ingestions or overdoses. The World Health Organization provides a listing of international poison centers at its website: www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html

Further information on pesticide intoxication can be obtained in the United States from National Pesticide Telecommunications Network at: 1-800-858-7378 or http://npic.orst.edu.sci-hub.cc/ (outside the United States: 1-806-743-3091).

SUMMARY AND RECOMMENDATIONS — While the diagnosis of organophosphorus agent poisoning is often not subtle, the management of these patients may be complex and protracted. All symptomatic patients should receive therapy with oxygen, atropine, an oxime (eg, pralidoxime), and a benzodiazepine. A summary table to facilitate emergent management is provided (table 1).

- Acute toxicity from organophosphorus agents presents with manifestations of cholinergic excess. The dominant clinical features of acute cholinergic toxicity include bradycardia, miosis, lacrimation, salivation, bronchorrhea, bronchospasm, urination, emesis, and diarrhea. (See 'Acute toxicity' above.)

- Ten to 40 percent of organophosphorus poisoned patients develop a distinct neurologic disorder 24 to 96 hours after exposure. This disorder consists of characteristic neurological findings including neck flexion weakness, decreased deep tendon reflexes, cranial nerve abnormalities, proximal muscle weakness, and respiratory insufficiency. (See 'Intermediate (neurologic) syndrome' above.)

- The diagnosis of organophosphate (OP) or carbamate poisoning is made on clinical grounds. In the absence of a known ingestion or exposure, the clinical features of cholinergic excess reflect the possibility of OP poisoning. Due to significant variability in toxicity and treatment, every effort should be made to precisely identify the agent. (See 'Diagnosis' above.)

- Moderately to severely poisoned patients with markedly depressed mental status require 100 percent oxygen and immediate tracheal intubation. In addition, patients who appear mildly poisoned may rapidly develop respiratory failure. Succinylcholine should be avoided when performing rapid sequence intubation in patients with OP poisoning. Bradycardia and hypotension are usually present in moderate to severe poisonings. Adequate volume resuscitation with isotonic crystalloid should be performed concomitantly with other resuscitative and diagnostic efforts. (See 'Initial resuscitation' above.)

- We recommend atropine therapy for all patients with any degree of possible cholinergic toxicity from OP or carbamate poisoning (Grade 1A). Atropine is started at a dose of 2 to 5 mg IV for adults and 0.05 mg/kg IV for children. If no effect is noted, the dose is doubled every three to five minutes until pulmonary muscarinic signs and symptoms are alleviated. (See 'Atropine' above.)
administered slowly over 30 minutes. Pralidoxime should **not** be administered without concurrent atropine. (See ‘Pralidoxime’ above.)

- In cases of topical exposure with potential dermal absorption, aggressive decontamination with complete removal of the patient’s clothes and vigorous irrigation of the affected areas should be performed. (See ‘Decontamination’ above.)

- Transfer of moderately to severely ill patients to a regional toxicology treatment center is encouraged.

Use of UpToDate is subject to the Subscription and License Agreement.

**REFERENCES**

53. Schexnader S, James LP, Keams GL, Farrar HC. The pharmacokinetics of continuous infusion pralidoxime in...


64. Davies JO, Eddleston M, Buckley NA. Predicting outcome in acute organophosphorus poisoning with a poison severity score or the Glasgow coma scale. QJM 2008; 101:371.


Topic 339 Version 17.0
General structures of organophosphate (left) and carbamate (right) agents

The variable R1 and R2 groups are composed of either methyl (CH3) or ethyl (CH3CH2) moieties. The leaving group is generally an oxime or an aromatic group. Organophosphorones are similar to organophosphates, but they lack a sulfur atom, and are instead bound to four oxygen molecules.

Graphic 57527 Version 1.0
Organophosphate and carbamate poisoning: Rapid overview

To obtain emergent consultation with a medical toxicologist, call the United States Poison Control Network at 1-800-222-1222, or access the World Health Organization’s list of international poison centers (www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html).

Clinical syndromes

<table>
<thead>
<tr>
<th>Acute toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generally manifests in minutes to hours</td>
</tr>
<tr>
<td>Evidence of cholinergic excess</td>
</tr>
<tr>
<td>SLUDGE = Salivation, Lacrimation, Urination, Defecation, Gastric Emptying</td>
</tr>
<tr>
<td>BBB = Bradycardia, Bronchorrhea, Bronchospasm</td>
</tr>
<tr>
<td>Respiratory insufficiency can result from muscle weakness, decreased central drive, increased secretions, and bronchospasm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurs 24-96 hours after exposure</td>
</tr>
<tr>
<td>Bulbar, respiratory, and proximal muscle weakness are prominent features</td>
</tr>
<tr>
<td>Generally resolves in 1-3 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organophosphorus Agent-Induced Delayed Peripheral Neuropathy (OPIDN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually occurs several weeks after exposure</td>
</tr>
<tr>
<td>Primarily motor involvement</td>
</tr>
<tr>
<td>May resolve spontaneously, but can result in permanent neurologic dysfunction</td>
</tr>
</tbody>
</table>

Diagnostic evaluation of acute toxicity

Atropine challenge if diagnosis is in doubt (1 mg IV in adults, 0.01 to 0.02 mg/kg in children)

Absence of anticholinergic signs (tachycardia, mydriasis, decreased bowel sounds, dry skin) strongly suggests poisoning with organophosphate or carbamate

Draw blood sample for measurement of RBC acetylcholinesterase activity to confirm diagnosis

Treatment of acute toxicity

Deliver 100 percent oxygen via facemask; early intubation often required; avoid succinylcholine

Decontamination if ingestion within 1 hour give single dose activated charcoal, adult 50 g (1 g/kg in children) unless airway not protected or other contraindication. Aggressive dermal and ocular irrigation as needed. Bag/discard clothing.

Atropine 2 to 5 mg IV/IM/IO bolus (0.05 mg/kg IV in children)

Escalate (double) dose every 3-5 minutes until bronchial secretions and wheezing stop

TACHYCARDIA AND MYDRIASIS ARE NOT CONTRAINDICATIONS TO ATROPINE USE

Hundreds of milligrams may be needed over several days in severe poisonings

Inhaled ipratropium 0.5 mg with parenteral atropine may be helpful for bronchospasm; may repeat

Pralidoxime (2-PAM) 2 g (25 mg/kg in children) IV over 30 minutes; may repeat after 30 minutes or give continuous infusion if severe

Continuous infusion at 8 mg/kg/hour in adults (10 mg/kg/hour in children)

If no IV access, give pralidoxime 600 mg IM (15 mg/kg in children <40 kg). Rapidly repeat as needed to total of 1800 mg or 45 mg/kg in children.
Graphic 63540 Version 11.0
Chlorpyrifos structure

R₁
\[ \text{O} \]
R₂—O—P—O—⁻¹ (Leaving group)
S

[General Organophosphate Structure]

CH₃—CH₂—O—P—O
S
Cl

[Chlorpyrifos]

Graphic 74088 Version 1.0
Mechanism of action: Organophosphate and pralidoxime

Acetylcholinesterase (ACHE) inhibition by an organophosphorone agent

Inactivated ACHE

Nucleophilic attack of the phosphorylated ACHE active site by pralidoxime

Phosphorylated pralidoxime

Reactivation of ACHE by pralidoxime

Graphic 78828 Version 1.0
Neurologic effects of organophosphate and carbamate agents

ACH: acetylcholine; Epi: epinephrine; NE: norepinephrine; NMJ: neuromuscular junction.

Graphic 75227 Version 3.0
Agents associated with organophosphorous induced delayed neuropathy

- Chlorpyrifos
- Leptophos
- Malathion
- Mephos
- Mipafox
- Trichlorfon
- Triorthocresylphosphate (TOCP)

Chlorpyrifos

---

Graphic 66967 Version 2.0
Contributor Disclosures


Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy