Insecticides, Herbicides, and Rodenticides

Robert D. Cannon and Anne-Michelle Ruha

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In the United States in 2008, 4642 exposures to OP compounds and 2644 exposures to carbamates were reported to the National Poison Data System of the American Association of Poison Control Centers.

PATHOPHYSIOLOGY

The clinical severity and toxicodynamics vary according to the agent, the route of absorption, and whether the exposure was intentional. Regardless of these factors, the toxicologic mechanism of acetylcholinesterase (AChE) inhibition remains consistent. The end result is an excess of the neurotransmitter acetylcholine (ACh), which results in overstimulation of muscarinic and nicotinic receptors and production of a cholinergic toxidrome.

Under normal circumstances, ACh is hydrolyzed by AChE to yield acetic acid and choline. In the presence of OP insecticides, AChE is phosphorylated, whereas in the presence of carbamate insecticides, the enzyme is carbamylated. As a result, the rate of regeneration of active AChE is slowed, and its function is inhibited. Within 24 to 72 hours of OP poisoning, an alkyl group may dissociate from the AChE-OP complex and thereby result in “aging” of the AChE. Once aging occurs, reactivation of AChE is no longer possible, and only synthesis of new enzyme can restore activity. In the case of carbamate poisoning, breakdown of the carbamate-AChE complex occurs much more rapidly and aging does not occur (Box 146.1).

ACh accumulates in the autonomic nervous system at postganglionic muscarinic (parasympathetic and sympathetic) receptors and preganglionic nicotinic (sympathetic) receptors. It also accumulates at the neuromuscular junction and in the central nervous system (CNS). Overstimulation of these receptors is responsible for the cholinergic toxidrome seen with OP and carbamate insecticide poisoning (Table 146.1).

Organophosphate (OP) compounds and carbamates are used extensively worldwide for agricultural, industrial, and domestic pest control and, as a result, represent a significant public health issue in the developing world. An estimated 3 million poisonings and more than 200,000 deaths occur from OP compounds each year worldwide.

In the United States in 2008, 4642 exposures to OP compounds and 2644 exposures to carbamates were reported to the National Poison Data System of the American Association of Poison Control Centers.

KEY POINTS

- Organophosphorus and carbamate poisonings cause excessive stimulation of muscarinic and nicotinic receptors by acetylcholine, which can potentially lead to life-threatening bronchorrhea and bronchospasm.
- Aggressive airway management and liberal use of atropine are important in the management of both organophosphorus and carbamate poisoning.
- Only a nondepolarizing neuromuscular blocker, such as vecuronium or rocuronium, should be used for intubation. Succinylcholine is metabolized by plasma cholinesterase, and prolonged paralysis may result if it is used in the setting of organophosphate poisoning.
- Timely administration of pralidoxime is key to the treatment of organophosphorus poisoning, but pralidoxime is not indicated for carbamate poisoning.
- Unintentional pediatric ingestion of 4-hydroxycoumarins (superwarfarins) accounts for the vast majority of rodenticide exposures and rarely results in toxicity.
- Ingestion of an anticoagulant rodenticide should be considered when a child younger than 6 years has an elevated prothrombin time or bleeding without another explanation.
- The prothrombin time should be measured at 24 and 48 hours after large ingestions of 4-hydroxycoumarins.
- Because no specific antidote or pharmacologic intervention has proved beneficial in treating paraquat or diquat poisoning, early decontamination is the most important step.

ORGANOPHOSPHORUS COMPOUNDS AND CARBAMATES

EPIDEMIOLOGY

Organophosphate (OP) compounds and carbamates are used extensively worldwide for agricultural, industrial, and domestic pest control and, as a result, represent a significant public health issue in the developing world. An estimated 3 million poisonings and more than 200,000 deaths occur from OP compounds each year worldwide. In the United States in 2008, 4642 exposures to OP compounds and 2644 exposures to carbamates were reported to the National Poison Data System of the American Association of Poison Control Centers.
### Table 146.1 Effects of Organophosphorus and Carbamate Insecticides

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>TARGET TISSUE</th>
<th>CLINICAL EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic nervous system:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postganglionic muscarinic (parasympathetic)—</td>
<td>Gastrointestinal tract</td>
<td>Vomiting, diarrhea, cramping</td>
</tr>
<tr>
<td>&quot;DUMBBELS&quot; (defecation, urination, miosis,</td>
<td>Genitourinary tract</td>
<td>Urination</td>
</tr>
<tr>
<td>bronchorrhea, bradycardia, emesis, lacrimation,</td>
<td>Heart</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>salivation) or “SLUDGE” (salivation, lacrimation,</td>
<td>Lungs</td>
<td>Bronchorrhea, bronchospasm</td>
</tr>
<tr>
<td>urination, defecation, gastric secretions, emesis)</td>
<td>Eye</td>
<td>Miosis, lacrimation</td>
</tr>
<tr>
<td>Preganglionic muscarinic (sympathetic)</td>
<td>Salivary glands</td>
<td>Salivation</td>
</tr>
<tr>
<td></td>
<td>Sweat glands</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td></td>
<td>Adrenal glands</td>
<td>† Catecholamines—tachycardia</td>
</tr>
<tr>
<td>Central nervous system (nicotinic/muscarinic)</td>
<td>Brain</td>
<td>Agitation, seizures, coma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(organophosphates &gt; carbamates)</td>
</tr>
<tr>
<td>Neuromuscular junction (nicotinic)</td>
<td>Skeletal muscle</td>
<td>Weakness, fasciculations, paralysis</td>
</tr>
</tbody>
</table>
Insecticides, Herbicides, and Rodenticides

some OP insecticides after absorption (e.g., malathion). The mnemonic SLUDGE (salivation, lacrimation, urination, defecation, gastric secretions, emesis) has traditionally been used to describe the cholinergic toxidrome. However, the mnemonic DUMBBELLS (defecation, urination, miosis, bronchorrhea, bradycardia, emesis, lacrimation, salivation) is probably more appropriate because it includes the life-threatening conditions bronchorrhea and bradyarrhythmias, as well as miosis, the distinguishing feature.

The clinical effects are summarized in Table 146.1; only caveats in the clinical findings are emphasized here. Bronchorrhea occurs commonly with moderate to severe poisonings\(^6\) and can progress to pulmonary edema and respiratory failure. Miosis in the setting of cholinergic symptoms is fairly specific for OP and carbamate insecticide poisoning and may help make the diagnosis. Unfortunately, it is not consistently present.

Although the parasympathetic muscarinic effects are most often emphasized, certain sympathetic effects may predominate. Sinus tachycardia is more common than bradycardia,\(^4,5\) and mydriasis may even be seen.\(^3\) Nicotinic effects often predominate in mild cases and occur early in severe cases. Excessive nicotinic stimulation at the neuromuscular junction has effects that resemble the actions of a depolarizing neuromuscular blocking agent. Therefore, patients with OP or carbamate insecticide poisoning may exhibit muscle fasciculations and weakness. Paralysis occurs as the toxicity worsens, and the primary cause of death in acute poisonings is probably respiratory arrest secondary to paralysis and bronchorrhea.

One to 3 days after apparent resolution of the symptoms, patients may experience profound weakness and paralysis of the proximal muscles, neck flexor muscles, and cranial nerves. This development, termed the intermediate syndrome,\(^6\) is probably explained by ongoing AChE inhibition (Box 146.2).

Finally, carbamates produce peripheral effects similar to those of OP compounds, but generally to a much lesser extent. A distinguishing clinical feature of carbamate toxicity is the paucity of central effects, which is secondary to their poor penetration of the CNS.

<table>
<thead>
<tr>
<th>BOX 146.1 Effects of Organophosphate and Carbamate on Acetylcholinesterase (AChE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organophosphate + AChE = phosphorylated AChE</td>
</tr>
<tr>
<td>Carbamate + AChE = carbamylated AChE</td>
</tr>
<tr>
<td>These complexes inactivate AChE and allow acetylcholine to sit on the nicotinic and muscarinic receptors and produce the symptoms of toxicity.</td>
</tr>
<tr>
<td>Three things can happen to the phosphorylated or carbamylated AChE:</td>
</tr>
<tr>
<td>• Breakdown of the complex (occurs more rapidly with carbamate) to release active AChE</td>
</tr>
<tr>
<td>• Complete binding and inactivation (aging), which occurs within 24 to 72 hours (with organophosphates) and requires that new AChE be produced</td>
</tr>
<tr>
<td>• Reactivation by a strong nucleophile such as pralidoxime</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BOX 146.2 Paralysis Seen After Organophosphate Poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
</tr>
<tr>
<td>Acute paralysis secondary to constant depolarization at the neuromuscular junction</td>
</tr>
<tr>
<td>Type II (Intermediate Syndrome)</td>
</tr>
<tr>
<td>• Develops 1 to 3 days after resolution of the acute organophosphate poisoning symptoms</td>
</tr>
<tr>
<td>• Manifested as paralysis and respiratory distress secondary to weakness of the proximal muscles, neck flexor muscles (with relative sparing of the distal muscle groups), and cranial nerve palsies</td>
</tr>
<tr>
<td>• Lasts for 4 to 18 days and may require mechanical ventilation</td>
</tr>
<tr>
<td>• Results from ongoing acetylcholinesterase inhibition or suboptimal treatment</td>
</tr>
<tr>
<td>Type III (Organophosphate-Induced Delayed Polyneuropathy)</td>
</tr>
<tr>
<td>Manifested 2 to 3 weeks after exposure</td>
</tr>
<tr>
<td>Results from inhibition of target esterase</td>
</tr>
<tr>
<td>Characterized by distal muscle weakness with relative sparing of the neck muscles, cranial nerves, and proximal muscle groups</td>
</tr>
<tr>
<td>Recovery can take up to 12 months</td>
</tr>
</tbody>
</table>

Differential Diagnosis and Medical Decision Making

A detailed history in a patient with signs and symptoms of cholinergic excess often elucidates exposure to OP or carbamate insecticides. The diagnosis of OP or carbamate insecticide poisoning is therefore usually straightforward; however, certain clinical aspects may be mimicked by other entities. Table 146.2 is a partial list of other agents or diagnoses to consider.

All patients with potential OP poisoning should undergo erythrocyte (red blood cell [RBC], or true) cholinesterase and plasma (pseudo) cholinesterase measurement from specimens obtained after arrival at the emergency department (ED). Though not often useful or necessary for making a diagnosis in the ED, the results of this measurement may help guide continued therapy. RBC cholinesterase hydrolyzes ACh and correlates with toxicity, whereas plasma cholinesterase is the first to decline and may be a more sensitive marker of exposure.\(^7\) Both substances should be measured because one may exhibit greater inhibition than the other, depending on the specific OP to which the patient was exposed. Box 146.3 summarizes the tests that may be helpful in evaluating a patient with moderate to severe toxicity.

Cholinesterase values may prove useful in diagnosing OP toxicity if the history or findings on physical examination are unclear. The values must be interpreted with caution, however. There is great interindividual and intra-individual variation in baseline cholinesterase values. A patient may have a 50% depression in cholinesterase activity, yet the level still falls within the “normal” reference range. This makes cholinesterase measurements of limited value in the initial diagnosis of
SECTION XV  TOXICOLOGIC EMERGENCIES

poisoning. The levels are helpful in confirming poisoning only if they are extremely low or undetectable at initial evaluation. The finding of “normal” levels does not necessarily rule out poisoning if the history and clinical picture are otherwise supportive.

TREATMENT

Treatment focuses on aggressive airway management, liberal use of atropine for control of excessive airway secretions, and in the case of OP compounds, early administration of the antidote pralidoxime. Prompt recognition of toxicity and early intervention usually result in complete recovery.

The treatment algorithm for OP and carbamate insecticide poisoning is summarized in Figure 146.1. The first step is adequate decontamination of the patient by removal of wet clothing and washing of contaminated skin with soap and water. ED personnel should wear gowns, gloves, and masks to prevent exposure to contaminated body fluids.

As the patient is being decontaminated, the emergency physician (EP) should focus on the ABCs (airway, breathing, circulation), with particular attention paid to early airway management for copious secretions, seizures, coma, severe weakness, and paralysis. If intubation is necessary, only a nondepolarizing neuromuscular blocking agent, such as vecuronium or rocuronium, should be used. Succinylcholine is metabolized by plasma cholinesterase, so prolonged paralysis may result if this agent is used a patient with OP poisoning.

Treatment should next be directed at controlling muscarinic activity. Atropine is the drug of choice and should be administered intravenously at a dose of 2 to 5 mg (pediatric dose, 0.05 mg/kg) every 3 to 5 minutes, with the end point being control of respiratory secretions. Tachycardia is not a contraindication to atropine administration. Mild poisonings may resolve with just 1 to 2 mg of atropine, and severe poisonings may require more than 1000 mg. Large doses of atropine may lead to antimuscarinic CNS toxicity. If such toxicity occurs, glycopyrrolate (1 to 2 mg; pediatric dose, 0.025 mg/kg) can be used in place of atropine.

Pralidoxime is the antidote for OP insecticide poisoning. Although its efficacy may vary according to the structure of the OP compound, it should be given to all OP-poisoned patients. It works by increasing the rate of AChE regeneration. It is a common belief that pralidoxime is not beneficial if given after 24 hours because of the “aging” of AChE. However, OP insecticides have been detected in blood weeks after exposure. Their presence may be secondary to redistribution from fat. Therefore, late pralidoxime therapy may still be of benefit. The adult dose is 1 to 2 g via the intravenous (IV) route delivered over a 15- to 30-minute period followed by a continuous infusion of 500 mg/hr. Pediatric dosing consists of a 25- to 50-mg/kg load followed by a 10- to 20-mg/kg/hr infusion. Pralidoxime is not indicated for carbamate poisoning, which is usually mild and self-limited.

ORGANOCHLORINES

Epidemiology

Organochlorines are heavily chlorinated aromatic compounds that are nonvolatile and poorly water soluble. They are...
Insecticides, Herbicides, and Rodenticides

Insect IcIdes, Herb IcIdes, and rodent IcIdes divided into four classes on the basis of their structural characteristics, and they vary tremendously with respect to dermal absorption, lipid solubility, and toxic doses. The clinical toxicity, which is similar for each of the classes, is summarized in (Table 146.3).

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**Table 146.3**

**Organophosphate exposure**

**Inhalation**
- 1. Remove and bag clothing
- 2. Assess ABCs

**Ingestion**
- 1. Wash skin with soap and water; irrigate eyes if exposed
- 2. Assess ABCs

**Dermal**
- Wash skin with soap and water; irrigate eyes if exposed

**Establish IV access and intubate if necessary**

**(DO NOT use succinylcholine, only nondepolarizing agents)**

**Laboratory tests** (RBC and plasma cholinesterase level, CBC, chemistry panel, liver profile, ABG, ECG, CXR)

**Treatment takes priority over evaluation**

**Fig. 146.1** Treatment algorithm for organophosphorus insecticide poisoning. 

**ABGs**, Airway, breathing, and circulation; **ABG**, arterial blood gas determination; **CBC**, complete blood count; **CXR**, chest radiograph; **ECG**, electrocardiography; **ICU**, intensive care unit; **IV**, intravenous; **RBC**, red blood cell.

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**Fig. 146.1** Treatment algorithm for organophosphorus insecticide poisoning. 

**Inhalation**
- 1. Remove and bag clothing
- 2. Assess ABCs

**Ingestion**
- 1. Wash skin with soap and water; irrigate eyes if exposed
- 2. Assess ABCs

**Dermal**
- Wash skin with soap and water; irrigate eyes if exposed

**Establish IV access and intubate if necessary**

**(DO NOT use succinylcholine, only nondepolarizing agents)**

**Laboratory tests** (RBC and plasma cholinesterase level, CBC, chemistry panel, liver profile, ABG, ECG, CXR)

**Treatment takes priority over evaluation**

**1. Atropine, 2-5 mg IV (children: 0.05 mg/kg)**
- even if tachycardic

**2. Pralidoxime, 1-2 g over 30 min, then**
- 500-mg/hr infusion (children: 25-50 mg/kg, then 10-20 mg/kg/hr). **DO NOT** give for carbamate poisoning

**Establish IV access and intubate if necessary**

**Fig. 146.1** Treatment algorithm for organophosphorus insecticide poisoning. 

**Inhalation**
- 1. Remove and bag clothing
- 2. Assess ABCs

**Ingestion**
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- 2. Assess ABCs

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- Wash skin with soap and water; irrigate eyes if exposed

**Establish IV access and intubate if necessary**

**(DO NOT use succinylcholine, only nondepolarizing agents)**

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- 500-mg/hr infusion (children: 25-50 mg/kg, then 10-20 mg/kg/hr). **DO NOT** give for carbamate poisoning

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**See Table 146.3, Major Organophosphorus Insecticides, at www.expertconsult.com**
## Table 146.3 Major Organochlorine Insecticides

<table>
<thead>
<tr>
<th>CLASS</th>
<th>PRODUCT</th>
<th>DERMAL ABSORPTION</th>
<th>ORAL TOXICITY</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexachlorocyclohexane</td>
<td>Lindane</td>
<td>High</td>
<td>Moderate</td>
<td>Central nervous system (CNS) excitation, seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichlorodiphenylethanes</td>
<td>DDT</td>
<td>Low</td>
<td>Moderate</td>
<td>CNS excitation</td>
</tr>
<tr>
<td></td>
<td>Methoxychlor</td>
<td>Low</td>
<td>Low</td>
<td>Less toxic than dichlorodiphenyltrichloroethane (DDT)</td>
</tr>
<tr>
<td>Cyclodienes</td>
<td>Aldrin</td>
<td>High</td>
<td>High</td>
<td>Metabolized to dieldrin</td>
</tr>
<tr>
<td></td>
<td>Dieldrin</td>
<td>High</td>
<td>High</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Endrin</td>
<td>High</td>
<td>Highest</td>
<td>Rapid-onset seizures</td>
</tr>
<tr>
<td></td>
<td>Chlordane</td>
<td>High</td>
<td>Moderate</td>
<td>Early and late seizures</td>
</tr>
<tr>
<td></td>
<td>Endosulfan</td>
<td>High</td>
<td>High</td>
<td>Sulfur odor</td>
</tr>
<tr>
<td></td>
<td>Toxaphene</td>
<td>Low</td>
<td>Moderate-high</td>
<td>Seizures, often mixed with parathion</td>
</tr>
<tr>
<td>Chlordecone and mirex</td>
<td>Chlordecone</td>
<td>High</td>
<td>Moderate</td>
<td>“Kepone shakes,” no seizures</td>
</tr>
<tr>
<td></td>
<td>Mirex</td>
<td>High</td>
<td>Low</td>
<td>Same as above</td>
</tr>
</tbody>
</table>
Section XV — Toxicologic Emergencies

Most organochlorines have been banned in North America because of concern about their environmental persistence and bioconcentration. The only organochlorine still in common use in the United States is lindane (Kwell). It is used in agriculture as a seed treatment and medicinally as a topical scabicide in a 1% formulation. Toxicity from therapeutic lindane application is exceedingly rare, and most clinically relevant toxicity events occur as a result of inappropriate dermal application or ingestion.\textsuperscript{11-13}

Pathophysiology

Lindane acts as an antagonist of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS.\textsuperscript{14} Toxicity results from loss of inhibitory tone and subsequent CNS hyperexcitability.

Presenting Signs and Symptoms

Symptoms, which can occur within 30 minutes of the ingestion of lindane,\textsuperscript{12} often include nausea and vomiting. With excessive or repeated topical applications, the onset of symptoms may be delayed from a few hours up to 4 to 5 days.\textsuperscript{11,14} CNS excitation is the hallmark of lindane toxicity. It is manifested by paresthesias, agitation, tremor, myoclonus, hallucinations, and most important, seizures. Seizures may occur suddenly and without prodrome. Complications of prolonged seizures may develop, including respiratory failure, metabolic acidosis, rhabdomyolysis, and hyperthermia.

Differential Diagnosis and Medical Decision Making

The differential diagnosis for suspected lindane poisoning is extremely broad because it can potentially include any cause of seizures. Appropriate, therapeutic use of lindane is not expected to produce toxicity. Unless a patient has ingested lindane before the onset of symptoms, an alternative explanation should be sought to explain the seizures. Although some laboratories can measure lindane levels, the results will not be immediately available to the EP. Therefore, the diagnosis is primarily clinical.

Treatment

No specific antidote is available for lindane toxicity. Although activated charcoal can be considered early after ingestion, it may be dangerous in a patient who may have seizures without warning. The mainstay of treatment is supportive. Benzodiazepines should be used to treat seizures. If that therapy is unsuccessful, barbiturates (phenobarbital) should be administered. As with other toxin-induced seizures, phenytoin is not indicated.

All symptomatic patients with lindane toxicity should be admitted to the hospital. Asymptomatic patients seen after the ingestion of lindane may be observed for 6 hours from the time of ingestion; if no symptoms develop, the patient can be medically cleared.

Pyrethrins and Pyrethroids

Epidemiology

Pyrethrins are naturally occurring esters of chrysanthemum resin that possess insecticidal activity, whereas pyrethroids are synthetic derivatives of pyrethrins. Exposures to these agents are commonly reported to poison centers. Most are accidental, and serious clinical effects are rare.\textsuperscript{7}

Pathophysiology

Pyrethrins and pyrethroids delay closure of sodium channels. The delay results in prolonged depolarization, repetitive firing, and eventually conduction blockade.\textsuperscript{15} Some pyrethroids may inhibit GABA chloride channels, but it is unlikely that such inhibition plays a significant role in toxicity.

Presenting Signs and Symptoms

Most cases of clinically relevant toxicity from pyrethrins result from pulmonary allergic reactions rather than from direct toxic effects. The signs and symptoms are similar to those of asthma exacerbations and consist of wheezing, cough, dyspnea, and chest pain. Most reactions are mild and easily treated. However, fatal status asthmaticus has been reported with exposure to pyrethrin-containing shampoo.\textsuperscript{16,17}

Accidental or occupational exposure to pyrethrins usually produces minimal, if any, toxicity. The most common symptoms reported are facial paresthesias, dizziness, headache, nausea, anorexia, and fatigue.\textsuperscript{18} Massive exposures or large intentional ingestions may lead to more serious manifestations: seizures, altered mental status, coma, respiratory failure, and death.

Differential Diagnosis and Medical Decision Making

The differential diagnosis for pyrethrin and pyrethroid poisoning includes any other cause of allergic or asthmatic symptoms in most cases, but because treatment is the same, it is not important to know whether the exposure caused the symptoms. If the symptoms are neurologic or gastrointestinal, the differential diagnosis is quite broad; unfortunately, no laboratory or other test will help in differentiation.

Treatment

Activated charcoal may be given to a patient initially seen within 1 hour of a large oral ingestion of pyrethrin or pyrethroid. Skin decontamination is accomplished with soap and water. Pyrethrin-induced bronchospasm is treated with oxygen, β-adrenergic agonists, and corticosteroids as needed. No specific antidote is available, and the symptoms resolve with supportive care.
**FIPRONIL**

**EPIDEMIOLOGY**
Fipronil is a relatively new insecticide that was first introduced in 1996, and over the past several years it has increasingly been used to control common household insects, in addition to being used in flea and tick treatment for pets. Until recently, limited human toxicity data existed. It is commonly found in Frontline and Maxforce products.

**PATHOPHYSIOLOGY**
Fipronil acts as a GABA antagonist, which leads to excessive CNS excitation and death of the insect. It is more specific for the insect GABA receptor than it is for its mammalian counterpart.

**PRESENTING SIGNS AND SYMPTOMS**
The majority of human exposures are unintentional and most commonly result in neurologic symptoms such as dizziness and headache. Ocular and upper respiratory irritation has been reported commonly in addition to nausea and vomiting. More severe exposures or large intentional ingestions can cause CNS excitation and seizures.

**DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING**
Again, depending on the neurologic or gastrointestinal symptoms, the differential diagnosis may be broad and cannot be narrowed with any laboratory or diagnostic test. A history of exposure or potential exposure remains the most important key.

**TREATMENT**
Treatment of fipronil exposure remains primarily supportive and symptomatic. In patients with significant exposure who arrive at the ED in a state of CNS excitation or with seizures, the mainstay of treatment is airway protection and liberal use of benzodiazepines for sedation and control of the seizures.

**RED FLAGS**
**Insecticides**
Miosis in the setting of cholinergic symptoms, though not consistently present, is fairly specific for organophosphate and carbamate insecticides and may help make the diagnosis. Although the parasympathetic muscarinic effects are most often emphasized, certain sympathetic effects may predominate (sinus tachycardia is more common than bradycardia, and mydriasis may be seen). Nicotinic effects often predominate in mild cases and occur early in severe cases. “Normal” cholinesterase levels do not necessarily rule out poisoning if the history and clinical picture are otherwise indicative. Symptoms can occur within 30 minutes of the ingestion of lindane, but with excessive or repeated topical applications, the onset of symptoms may be delayed from a few hours to 4 to 5 days.

**PARAQUAT AND DIQUAT**

**EPIDEMIOLOGY**
Paraquat and diquat belong to the bipyridyl class of herbicides. They are both commonly used worldwide for weed control in the agricultural, horticultural, and forestry industries, and paraquat is marketed in more than 130 countries. Both compounds are available for home and commercial use in varying concentrations. Paraquat is commonly sold as a 0.2% solution for home use but can be found in 10% to 24% concentrated commercial solutions. Paraquat and diquat account for only 4.9% of herbicide poisonings but are responsible for more than 50% of herbicide-related deaths. This fact points to the extremely toxic nature of these compounds. Most serious toxicity events and deaths are secondary to intentional ingestion.

**PATHOPHYSIOLOGY**
Paraquat is rapidly absorbed after ingestion and is concentrated in type I and type II alveolar epithelial cells. It is subsequently reduced to a free radical, which then reacts with oxygen to form a superoxide anion ($O_2^-$). This anion then may form $H_2O_2$, which in the presence of Fe$^{3+}$, will generate highly toxic radicals.
reactive species such as the hydroxyl radical (OH). These reactive molecules cause lipid peroxidation and cellular destruction.\(^{22}\) Initially, acute alveolitis may occur. Later, proliferative changes and pulmonary fibrosis are seen. Although paraquat concentrates mostly in the lungs, it is also distributed throughout the entire body and causes cellular destruction in multiple organs.

The pathophysiologic mechanism of diquat is similar to that of paraquat. Diquat does not concentrate in the lungs, however, and does not produce pulmonary fibrosis.\(^{23}\)

### PRESENTING SIGNS AND SYMPTOMS

Paraquat poisoning can be classified as mild, moderate, or severe according to the amount ingested.\(^{21}\) Physical examination findings are summarized in Table 146.4. Mild poisonings, which occur when small amounts of dilute preparations are ingested, are characterized by the development of gastrointestinal symptoms without other organ toxicity. As the amount of paraquat or diquat ion ingested rises, worsening gastrointestinal effects are seen, including severe oropharyngeal, esophageal, and gastric ulceration. Large ingestions produce renal and hepatic failure within a few days. Paraquat toxicity results in pulmonary fibrosis and refractory hypoxemia several days to weeks after ingestion, and death usually occurs within a few weeks. Massive ingestions cause multiorgan failure and death within a few days. Diquat toxicity does not produce pulmonary fibrosis. Diquat ingestion has been associated with brainstem infarction.\(^{23}\) Effects from dermal exposure to paraquat and diquat are usually mild, but ulcers and blistering can occur with highly concentrated formulations.

### DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING

A qualitative urine test can be performed to aid in the diagnosis of paraquat or diquat poisoning. When alkaline sodium dithionate is added to urine, the color turns blue when paraquat is present and blue-green in the presence of diquat. Quantitative plasma measurements may also be obtained to confirm exposure and determine prognosis. Neither of these tests may be readily available in the emergency setting. Therefore, the diagnosis is often based on the history alone. The differential diagnosis of paraquat and diquat poisoning is wide and includes exposure to other caustic substances.

### TREATMENT

No specific antidote or pharmacologic intervention has been proven to affect outcome after paraquat or diquat poisoning. Early decontamination is the most important step in initial management and may be futile after large ingestions because of rapid absorption. There is little clinical or experimental evidence for the use of gastric lavage, and the procedure may even worsen the oral or esophageal ulceration. Therefore, activated charcoal (1 to 2 g/kg) is the agent of choice for gastric decontamination. Other agents, such as diatomaceous fuller’s earth (1 to 2 g/kg in a 30% aqueous solution) and bentonite (1 to 2 g/kg of a 7% aqueous solution), have been used but are not as likely to be available to the EP, nor do they provide any advantage over charcoal. Gastric decontamination should be initiated as soon as possible.

Supportive care should be provided, with airway protection and ventilation being paramount. Supplemental oxygen may worsen the toxicity by accelerating the damage caused by oxygen radicals. It is generally accepted that supplemental oxygen be withheld until the PaO\(_2\) value falls below 40 to 50 mm Hg. IV fluids should be given to ensure normal urine output and analgesics provided for the pain associated with mucosal ulcerations. Many other pharmacologic treatments of paraquat poisoning have been investigated, but none have proved useful.\(^{22}\) Hemoperfusion and hemodialysis are effective in removing paraquat from the blood, but neither improves the prognosis.

### CHLORPHENOXY HERBICIDES

**Epidemiology**

Chlorophenoxy herbicides are widely used to control the growth of broad-leaved weeds in pastures and crop fields and

<table>
<thead>
<tr>
<th>DEGREE</th>
<th>AMOUNT INGESTED</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&lt;20 mg/kg paraquat ion</td>
<td>Asymptomatic or gastrointestinal symptoms Patients recover fully</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>20-40 mg/kg</td>
<td>Oropharyngeal erythema and ulcerations may occur Vomiting and diarrhea Acute renal failure and hepatic dysfunction within 24 hr Pulmonary fibrosis in all patients, but may be delayed days to weeks Most die within 2-3 wk</td>
</tr>
<tr>
<td>Fulminant</td>
<td>&gt;40 mg/kg</td>
<td>Definite ulceration of the oropharynx Rapid development of multiorgan failure Severe lung injury, cerebral edema, seizures, renal failure, hepatic necrosis, pancreatic necrosis, cardiovascular collapse 100% mortality Death in 24 hr to a few days after the overdose</td>
</tr>
</tbody>
</table>
along public streets. Poisoning is uncommon, and most ED encounters consist of accidental dermal or inhalational exposure, for which serious systemic toxicity is rare. However, intentional ingestion of these compounds carries high morbidity and mortality. From 1962 to 2004, 69 cases of ingestion of chlorphenoxyl herbicides alone (excluding other pesticides as coingestants) were reported. One third of the patients in these reports died.24

**PATHOPHYSIOLOGY**

The pathophysiology of chlorphenoxyl herbicide toxicity involves three mechanisms. First, a dose-dependent disruption of cell membranes is thought to be responsible for mediation of CNS toxicity through disruption of the blood-brain barrier. Second, these compounds may form analogues of acetyl coenzyme A (CoA) and thereby disrupt its role in cellular metabolism. Because acetyl CoA is involved in formation of the neurotransmitter ACh, false cholinergic transmitters may be formed. A third mechanism of toxicity results from uncoupling of oxidative phosphorylation, which leads to depletion of cellular adenosine triphosphate.25

**PRESENTING SIGNS AND SYMPTOMS**

Vomiting is common early after ingestion and may be accompanied by abdominal pain and diarrhea. Hypotension may occur secondary to volume loss, peripheral vasodilation, and direct myocardial toxicity. Severe ingestions are often associated with a rapid onset of coma. Other neurologic features that have been reported are hyperreflexia, hypertonia, seizures, hallucinations, clonus, and ataxia.24,25 Peripheral neuromuscular effects include weakness, loss of deep tendon reflexes, and fasciculations. Common metabolic effects are acidosis, hyperthermia, and rhabdomyolysis.

**DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING**

The diagnosis is made by obtaining a history of ingestion of or exposure to these agents. Plasma levels can be measured, but the results are not available in the emergency setting. When the history is lacking, the diagnosis is difficult to make because the differential diagnosis includes any potential cause of metabolic acidosis, myopathy, changes in mental status, and gastroenteritis.

**TREATMENT**

Most patients can be managed with supportive care alone. Activated charcoal should be given if the patient is seen within 1 hour of a large ingestion. Other supportive measures are airway protection, IV fluids, and benzodiazepines for seizures, fasciculations, hyperreflexia, or clonus. Alkaline diuresis has been reported to reduce the half-life of 2,4-dichlorophenoxyacetic acid (2,4-D).26 Although hemodialysis and resin hemoperfusion enhance elimination of 2,4-D, no controlled trials have been conducted to assess whether these measures change the outcome. These modalities should be considered only for severe poisonings.

**GLYPHOSATE**

Glyphosate is a widely used herbicide with formulations that range from a 1% household concentration to a 41% concentrate for commercial use. In addition, many of the commercial formulations are mixed with surfactants, which themselves produce toxicity by destroying mitochondrial cell walls and interfering with cellular energy production. The amine surfactants are also highly alkaline and corrosive and thus contribute to much of the toxicity of glyphosate. Unintentional or small ingestions of glyphosate typically produce only mild gastrointestinal symptoms. An exception occurs with glyphosate-trimesium (Touchdown), which has produced rapid death after small ingestions.27 Most cases of significant toxicity result from intentional ingestion of the concentrated formulation of Roundup (41% glyphosate and 15% polyoxyethyleneamine surfactant). Common features are corrosive effects, such as oropharyngeal ulcers, dysphagia, abdominal pain, and vomiting. Significant laryngeal injury may lead to aspiration and lung injury. Metabolic acidosis is common with large ingestions of concentrated formulations. Hypovolemia and hypoperfusion may lead to secondary hepatic and renal insufficiency.28

**GLUFOSINATE**

Glufosinate is a nonselective herbicide used worldwide and marketed under the trade names BASTA, Ignite, Challenge, and Harvest. A glutamic acid analogue, glufosinate is combined with surfactants. As with glyphosate, ingestion of these products can lead to symptoms attributable to surfactants, such as corrosive injury, gastrointestinal symptoms, and acidosis. However, glufosinate is unique in that it may cause delayed onset of CNS toxicity. Ataxia, depressed level of consciousness, coma, and central apnea may develop 4 to 12
hours after ingestion. Delayed-onset seizures have been reported 29 hours after ingestion and may last for days. Treatment is supportive. Activated charcoal may be considered for patients seen within 1 hour after a large ingestion, but vomiting will probably limit its utility.

Rodenticides

Rodenticides vary greatly with respect to pathophysiology, signs and symptoms, degree of toxicity, and management. Because these poisonings are rarely encountered by EPs, a detailed discussion on each one is beyond the scope of this text. Some of the characteristics can be found in Table 146.5. Instead, attention is directed to the anticoagulant rodenticides warfarin and superwarfarin and the compound strychnine, which can be found in some rodenticides today.

ANTICOAGULANTS

EPIDEMIOLOGY

Anticoagulant rodenticides can be categorized as warfarins or superwarfarins. The warfarins were the first anticoagulant rodenticides introduced, and their toxicity in rodents and humans depended on repeated ingestion. They are virtually nontoxic after a single small ingestion. This characteristic made them attractive from a safety standpoint but rendered them poor rodenticides.

In the 1980s, the 4-hydroxycoumarins and indanediones were developed (see Table 146.6). For a listing of brands and concentrations). These potent, long-acting superwarfarins are lethal to rodents and toxic to humans after a single acute ingestion. These compounds are now responsible for the majority of exposures to anticoagulant rodenticides. Of the 14,425 rodenticide exposures reported to poison control centers in 2008, 11,146 involved superwarfarins. Most were unintentional ingestions in children younger than 6 years.

The warfarins and superwarfarins inhibit the synthesis of vitamin K1–dependent clotting factors (II, VII, IX, X) by blocking conversion of inactive vitamin K to the active form. Bleeding may occur when factor levels fall to 25% of baseline. Because factor VII has the shortest half-life (about 5 hours), a rise in the prothrombin time may be seen in three to four half-lives (15 to 20 hours after ingestion) and certainly will be present within 48 hours.

PRESENTING SIGNS AND SYMPTOMS

When a child is evaluated immediately after an unintentional ingestion, the child will be asymptomatic without signs of bleeding; 24 to 48 hours after a large ingestion, however, the child may have any manifestation of a coagulopathy, including, in order of decreasing frequency, ecchymosis, hematuria, uterine bleeding, gastrointestinal bleeding, epistaxis, spontaneous hematoma, gingival bleeding, hemoptysis, and hematemesis.

DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING

Ingestion of an anticoagulant rodenticide should be considered when a patient has an elevated prothrombin time or bleeding without other explanation. The differential diagnosis includes vitamin K deficiency, hemophilia or other factor deficiencies, and disseminated intravascular coagulation. The myriad causes of liver failure must also be considered, including viral hepatitis, alcoholic cirrhosis, hepatotoxic ingestions (e.g., acetaminophen, iron), and Wilson disease. A thorough laboratory evaluation aimed at sorting out these processes should be obtained, including a complete blood count, prothrombin and partial thromboplastin times, international normalized ratio, liver enzymes, fibrinogen and fibrin split products, measurements of coagulation factors (II, VII, IX, X), and a 50:50 mixing test. Brodifacoum and difenacoum measurements may be performed, but their results will not be immediately available to the EP.

TREATMENT

Figure 146.2 summarizes the management of warfarin or superwarfarin poisoning, which depends on the timing, amount ingested, and symptomatology. Accidental ingestions of less than one box of 4-hydroxycoumarin are unlikely to result in clinically significant toxicity and may be managed without gastric decontamination or laboratory evaluation unless signs of bleeding occur. Patients who ingest one or more boxes should be given activated charcoal if they are seen within 1 hour of ingestion. Acute hemorrhage is managed with oxygen and IV crystalloids to replace losses of volume. Fresh frozen plasma should be administered to patients with active bleeding and coagulopathy. Vitamin K1 is given at doses of 1 to 5 mg in children and 10 mg in adults. It may be administered intravenously at no more than 1 mg/min to reduce the likelihood of anaphylactoid reactions. Oral or subcutaneous administration is also acceptable.
### Table 146.5 Characteristics of Some Rodenticides

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>CLINICAL CHARACTERISTICS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium monofluoroacetate, fluoroacetamide</td>
<td>Vomiting 2-20 hr after exposure, acidosis, coma, seizures, hypokalemia, hypocalcemia</td>
<td>Supportive; intravenous fluids (IVF), benzodiazepines for seizures, bicarbonate for refractory acidosis</td>
</tr>
<tr>
<td>Zinc phosphide</td>
<td>Gastrointestinal distress within 30 min, cough, dyspnea, acidosis, seizures, coma</td>
<td>Supportive; IVF, benzodiazepines for seizures, bicarbonate for refractory acidosis</td>
</tr>
<tr>
<td>Yellow phosphorus</td>
<td>Dermal burns, “smoking” vomitus, diarrhea, and cardiovascular collapse in severe cases</td>
<td>Supportive; gastric lavage with 0.1% potassium permanganate suggested</td>
</tr>
<tr>
<td>ANTU (α-naphthyl-thiourea)</td>
<td>Possible pulmonary edema</td>
<td>Supportive; observe for the development of pulmonary edema</td>
</tr>
</tbody>
</table>

### Table 146.6 Anticoagulant Rodenticide (Superwarfarin) Brands and Concentrations

<table>
<thead>
<tr>
<th>RODENTICIDE</th>
<th>CONCENTRATIONS (%)</th>
<th>SELECTED BRAND NAMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Hydroxycoumarins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brodifacoum</td>
<td>0.005</td>
<td>D-Con Mouse, Talon, Talon G, Havoc</td>
</tr>
<tr>
<td>Bromadiolone</td>
<td>0.005</td>
<td>Bromone, Super-Caid, Ratimus</td>
</tr>
<tr>
<td>Difenacoum</td>
<td>0.005</td>
<td>Endox, Endrocid, Racumin, Rodentin</td>
</tr>
<tr>
<td>Indanediones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorophacinone</td>
<td>0.005, 0.25, 2.5</td>
<td>Caid, Drat, Liphadione, Microzul, Rozol</td>
</tr>
<tr>
<td>Diphacinone</td>
<td>0.005-2.0</td>
<td>Diphacin, Promar, Ramik</td>
</tr>
<tr>
<td>Pindone</td>
<td>0.025-2.0</td>
<td>Pival, Pivacin, Pivalyn</td>
</tr>
</tbody>
</table>
Insecticides, Herbicides, and Rodenticides

**FOLLOW-UP, NEXT STEPS IN CARE, AND PATIENT EDUCATION**

All patients with signs and symptoms of bleeding should be admitted to the hospital for reversal of coagulopathy and control of bleeding. Those with severe or life-threatening hemorrhage warrant admission to the intensive care unit. Asymptomatic patients seen after ingestion can be discharged with arrangements to have blood specimens obtained for measurement of the prothrombin time on an outpatient basis in 24 and 48 hours.

**STRYCHNINE**

**EPIDEMIOLOGY**

Strychnine is a naturally occurring alkaloid derived from seeds of the tree *Strychnos nux-vomica*. Though rarely used as a rodenticide today, it is still available in some gopher, mouse, and rat poisons. It has also been found in certain traditional Cambodian home remedies. Strychnine is an odorless
crystalline white powder with a bitter taste that is well absorbed in the gastrointestinal tract.

**PATHOPHYSIOLOGY**

Strychnine blocks the postsynaptic binding of glycine in the spinal cord and brainstem. Because glycine is the major inhibitory neurotransmitter in these areas, disinhibition results in excessive stimulation of motor neurons.\(^\text{34}\)

**PRESENTING SIGNS AND SYMPTOMS**

Symptoms usually begin within 15 to 30 minutes of ingestion. Initial symptoms include a heightened sense of awareness and muscle spasms. As the toxicity progresses, the muscular hyperexcitability worsens. Minimal stimuli can produce severe muscle spasms, opisthotonos, and trismus, which can be indistinguishable from seizures. Patients generally maintain a clear sensorium before and after these episodes, an effect unique to strychnine ingestion.\(^\text{34}\) The complications of strychnine poisoning are secondary to muscle spasms and include hyperthermia, metabolic acidosis, and rhabdomyolysis. Death is usually the result of respiratory failure from spasm of the respiratory muscles.

**DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING**

The diagnosis is based on a history of exposure in a patient with the aforementioned signs and symptoms. If the history is unknown, the differential diagnosis includes stimulant intoxication, alcohol or benzodiazepine withdrawal, neuroleptic malignant syndrome, serotonin syndrome, salicylate intoxication, encephalitis, meningitis, and tetanus.

**TREATMENT**

Treatment is largely supportive, with a focus on airway protection and management of muscle spasms with benzodiazepines. Activated charcoal is unlikely to be of benefit given the rapid absorption and onset of symptoms. For mild symptoms, the patient should be administered diazepam or lorazepam and placed in a dark quiet environment to avoid stimuli. Airway and ventilatory status must be monitored closely and continuously because sudden deterioration can occur. Patients with severe symptoms should be intubated and paralyzed with a nondepolarizing neuromuscular blocker. They should then be aggressively sedated with benzodiazepines, propofol, or barbiturates. If this approach fails to control the muscle activity, continuous neuromuscular paralysis is an option. All symptomatic patients should be admitted to the intensive care unit.

**REFERENCES**

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES