CHAPTER 163

PESTICIDES

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PERSPECTIVE

Pesticides, a generic term used to refer to all pest-killing agents, include numerous chemicals intended for use as insecticides, herbicides, rodenticides, fungicides, and fumigants. Many of these chemicals are general protoplasmic poisons affecting a wide range of organisms, including humans. These chemicals can be organized in general classes with associated characteristic clinical pictures that are important to recognize because patients with acute (and occasionally chronic) exposures to these agents come to the emergency department. In addition, other pesticides with particularly unique mechanisms of toxic effects are described.

ORGANOPHOSPHATE AND CARBAMATE INSECTICIDES

The first organophosphate insecticide, triethyl pyrophosphate, was synthesized in 1859 but did not replace nicotine as a pesticide until World War II. After World War II, these compounds were used as chemical warfare agents, as organophosphorus and carbamate insecticides, and as medicinal agents. With concern about the long half-life of the organochlorine dichlorodiphenyltrichloroethane (DDT), causing it to accumulate in the environment, the organophosphate insecticides became the most common pesticides for home and industrial use. Since the increased awareness of terrorism in the 1990s, nerve agents have gained prominence as weapons of mass destruction.[1]

Principles of Disease

Organophosphorus insecticides are highly lipid soluble and are readily absorbed through dermal, gastrointestinal, and respiratory routes. This lipid solubility results in the buildup of organophosphorus compounds in body fat, and toxic systemic levels often occur from repeated low-level exposures. The parent compound and its metabolites are acetylcholinesterase inhibitors, and because many parent organophosphorus compounds are less potent than their metabolites (e.g., parathion to paraoxon), delayed onset of clinical toxicity can occur.

Organophosphorus pesticides work by persistently inhibiting the enzyme acetylcholinesterase, the enzymatic deactivator of the ubiquitous neurotransmitter acetylcholine. Because of the global penetration of organophosphorus compounds, inhibition occurs at tissue sites (true acetylcholinesterase and represented by erythrocyte or red blood cell [RBC] cholinesterase) and in plasma (circulating pseudocholinesterase).[2] Inhibition of cholinesterase results in the accumulation and subsequent prolonged effect of acetylcholine at a variety of neurotransmitter receptors, including sympathetic and parasympathetic ganglionic nicotinic sites, postganglionic cholinergic sympathetic and parasympathetic muscarinic sites, skeletal muscle nicotinic sites, and central nervous system sites (Fig. 163-1).

Clinical Features

Signs and Symptoms

The accumulation of acetylcholine results in the classic SLUDGE cholinergic syndrome, manifested by hyperactivity of cholinergic responses at the receptor sites indicated previously. The clinical syndrome of muscarinic acetylcholinesterase inhibition (Table 163-1) causes postganglionic acetylcholine-induced hollow end-organ general hypersecretion, resulting in clinical findings that include miotic pupils, lacrimation, rhinorrhea, sialorrhea, bronchorrhea, vomiting, diarrhea, and urinary incontinence. Bradycardia is a classic sign of the cholinergic syndrome, but the increased release of norepinephrine from postganglionic sympathetic neurons precipitated by excess cholinergic activity at sympathetic ganglia may result in normal or even tachycardic heart rates (nicotinic effect). Sympathetic hyperactivity can cause diffuse diaphoresis, although this response is mediated by cholinergic receptors at preganglionic (nicotinic) and postganglionic (muscarinic) sites. The most lethal components of acetylcholinesterase inhibition occur in the brain and neuromuscular junction. A combination of sympathetic stimulation, involvement of the *N*-methyl-D-aspartate (NMDA) receptor, and enhanced acetylcholine concentrations can induce seizures.[3] At the neuromuscular junction, excess acetylcholine causes hyperstimulation of the muscles with secondary paralysis, and when the diaphragm is affected, cholinesterase poisoning leads to respiratory arrest.[4]

Although the classic clinical picture of acute organophosphorus poisoning is impressive, toxicity from gradual, cumulative exposure may be much more subtle. These patients commonly exhibit vague confusion or other central nervous system complaints; mild visual disturbances; or chronic abdominal cramping, nausea, and diarrhea.

Complications

Seizures, pulmonary hypersecretion (bronchorrhea), and bronchoconstriction are prominent mechanisms of early morbidity and mortality in cases of poisoning from acetylcholinesterase inhibitors. Bronchorrhea is often incorrectly called noncardiogenic pulmonary edema because the origin of the excessive pulmonary fluids is airway secretions, not transudation of fluid across the alveolar-capillary membrane. The obstruction of upper and lower airways, the potential intrusion of these bronchial secretions

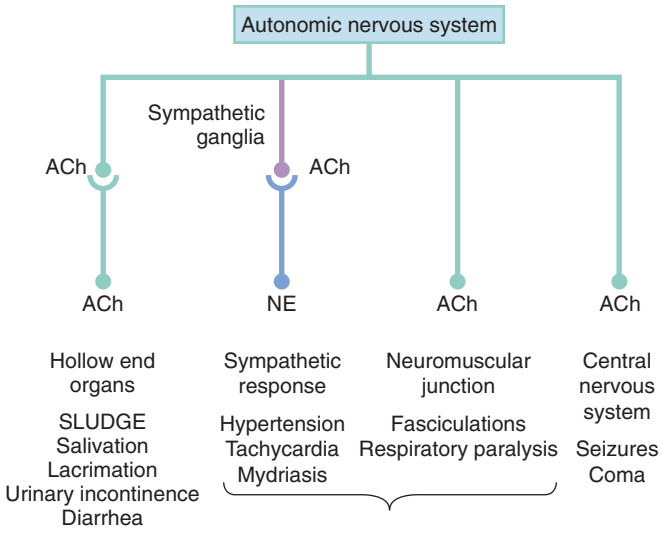

Figure 163-1. The autonomic nervous system comprises the sympathetic and parasympathetic nervous systems. The sympathetic nervous system is also known as the thoracolumbar outflow; the cell body lies in the spinal cord, and the first synapse occurs in the sympathetic ganglia. The neurotransmitter in this first synapse is acetylcholine (*ACh*, preganglionic), and the neurotransmitter in the postganglionic neuron with the target organ is norepinephrine (*NE*). In the parasympathetic nervous system (craniosacral outflow), nerves from the medulla and sacrum use ACh as the neurotransmitter in preganglionic and postganglionic target organs. The autonomic nervous system is divided further into the muscarinic and nicotinic receptors; atropine can block the muscarinic receptors but not the nicotinic receptors. The neuromuscular junction uses ACh as the effector neurotransmitter. In the brain, ACh is just one of several active neurotransmitters.

Table 163-1 SLUDGE Symptoms or DUMBELS

Salivation	**D**iarrhea/**D**iaphoresis
Lacrimation	**U**rination
Urinary incontinence	**M**iosis
Defecation	**B**radycardia/**B**ronchorrhea/**B**ronchospasm
Gastrointestinal cramps	**E**mesis
Emesis	**L**acrimation **S**alivation

into alveolar sacs, and bronchoconstriction produce hypoxia, which is the primary concern in the initial stages of poisoning.

Nicotinic hyperstimulation of skeletal muscle leads to significant morbidity and mortality associated with acetylcholinesterase inhibitor toxicity. Signs of skeletal muscle hyperactivity include involuntary twitches, fasciculations, and hyperactive reflexes. Muscle hyperactivity eventually progresses to muscle fatigue and paralysis, including the respiratory musculature and particularly the diaphragm.[4] Respiratory insufficiency may be delayed and result in death if it is not anticipated and corrected by mechanical or pharmacologic means.

Acetylcholinesterase inhibitors produce direct toxic effects on the central nervous system, leading to neurologic signs of confusion, combativeness, seizures, and coma. Status epilepticus may occur in severely poisoned patients. Structural central nervous system damage may occur if seizures are not terminated rapidly.[5]

A unique effect of organophosphorus insecticides results from "aging," the irreversible conformational change that occurs when the organophosphorus agent is bound to the cholinesterase enzyme for a prolonged time, causing clinical effects to persist for a prolonged time. On average, some aging for commercial organophosphorus agents will occur by 48 hours but may take longer. Once the enzyme has aged, an oxime antidote cannot regenerate the cholinesterase.

Diagnostic Strategies

Any patient with a clinically apparent cholinergic syndrome should be treated empirically without waiting for laboratory confirmation of decreased cholinesterase activity. Known or suspected exposure to cholinesterase inhibitors can be evaluated by ordering of plasma and erythrocyte (RBC) cholinesterase levels. However, these levels will not be readily available in most clinical settings. The patient's signs and symptoms should guide the management in the emergent time frame.

After acute exposures, the plasma cholinesterase levels decrease first, followed by decreases in RBC cholinesterase levels. The RBC cholinesterase level correlates best with activity at the nerve terminal.[2] Patients with chronic exposures may have a normal plasma cholinesterase level but have reduced RBC cholinesterase activity, which will confirm the poisoning. The true reflection of depressed cholinesterase activity is found in the RBC activity, and even a mild acute exposure may result in severe clinical poisoning. The RBC cholinesterase level recovers at a rate of 1% per day in untreated patients and takes approximately 6 to 12 weeks to normalize, whereas plasma cholinesterase levels may recover in 4 to 6 weeks. Other laboratory studies should focus on the evaluation of pulmonary, cardiovascular, and renal function and fluid and electrolyte balance. Patients presenting with no acidosis or only a metabolic acidosis on the arterial blood gas analysis have mortality lower than that of patients with a respiratory or mixed acidosis.[6]

Differential Diagnosis

Few toxins or other clinical conditions produce the same constellation of symptoms as acetylcholinesterase inhibitors. A species of mushroom, *Amanita muscaria,* historically has been mentioned in the differential diagnosis, but it actually contains alkaloids that usually produce an anticholinergic (antimuscarinic) syndrome. Conditions that induce excessive vagal responses (e.g., inferior wall myocardial infarction) may also produce some signs suggesting acetylcholinesterase inhibition, but other symptoms should make the primary cause apparent.

Management

Treatment is directed toward four goals: (1) decontamination, (2) supportive care, (3) reversal of acetylcholine excess at muscarinic sites, and (4) reversal of toxin binding at active sites on the cholinesterase molecule.

Decontamination should start in the out-of-hospital phase to prevent further absorption and subsequent toxicity and to protect care providers. Because dermal exposure is most likely, removal and destruction of clothing and thorough flushing of exposed skin may limit absorption and subsequent toxicity. Alternatively, dermal decontamination can be done with dry agents, such as military resins, flour, sand, or bentonite. Caregivers are at risk for contamination from splashes or handling of contaminated clothing. Treating personnel may be rotated to limit their exposure to the organophosphates.[4] Caregivers should use universal precautions, including eye shields, protective clothing, and nitrile or butyl rubber gloves. In the case of ingestion, gastrointestinal decontamination procedures are of questionable benefit because of the rapid absorption of these compounds. Profuse vomiting

and diarrhea are seen early in ingestion and may limit[7] or negate any beneficial effect of additional gastrointestinal decontamination.[8,9] The administration of activated charcoal after ingestion has no proven benefit in these poisonings.[10]

Equipment, but not skin, may be washed with a 5% hypochlorite solution to inactivate the cholinesterase inhibitor.

Because death is due to airway and respiratory failure, supportive care should be directed primarily toward airway management and include suctioning of secretions and vomitus, oxygenation, and, when necessary, ventilatory support. Succinylcholine can be used for intubation but may have an extremely prolonged duration (up to 3 to 7 hours) as it is metabolized by acetylcholinesterase, which is inhibited in this setting.[2] It is preferable to use a competitive neuromuscular blocking agent, such as rocuronium, for rapid sequence intubation in these patients, but increased dosing may be necessary. Although some authors have advocated the use of beta-blockers to control tachycardia, this may increase cardiovascular instability and worsen bronchospasm.[8,11] Most cardiovascular effects from organophosphates rarely require specific therapy.

The definitive treatment of acetylcholinesterase inhibition starts with atropine. A competitive inhibitor of acetylcholine at muscarinic receptor sites, atropine reverses the clinical effects of cholinergic excess at parasympathetic end-organs and sweat glands. Large doses of atropine may be required.[12] Data suggest that the more rapid the atropinization, the faster control is obtained.[8,9] Suggested dosing is 1 or 2 mg of atropine (0.02-0.05 mg/kg) intravenously, with doubling of each subsequent dose every 5 minutes until there is control of mucous membrane hypersecretion and the airway clears.[4,8,9,13] If intravenous access is not immediately available, atropine may be administered intramuscularly. Patients may require 200 to 500 mg of atropine intravenously during the first hour, followed by prolonged continuous infusions of 5 to 100 mg/hr to maintain adequate secretion control.[13] Tachycardia and mydriasis may occur at these doses, but they are not indications to stop atropine administration. The endpoint of atropinization is drying of respiratory secretions, easing of respiration, and mean arterial pressure greater than 60 mm Hg.[13] Animal evidence suggests that early rapid atropinization may limit seizure propagation and, in conjunction with diazepam, prevent status epilepticus.[5] Atropine is not active at nicotinic sites and does not reverse the skeletal muscle effects (e.g., muscle fatigue and respiratory failure).[2,9] Other anticholinergic medications, such as diphenhydramine or ophthalmic agents, may have benefit if atropine is scarce or unavailable; however, optimal intravenous dosing is not known.[14]

The second part of acetylcholinesterase inhibition treatment is the use of an oxime, such as pralidoxime (2-PAM, Protopam) or obidoxime (Toxogonin), to regenerate the organophosphate-acetylcholinesterase complex and to restore cholinesterase activity at muscarinic and nicotinic sites.[2,4,9,15] There are several dosing regimens; the most common dose of pralidoxime is 1 or 2 g intravenously (pediatric dose, 25-50 mg/kg); additional doses may be given on the basis of clinical response. The medication may be given in a bolus of 1 or 2 g intravenously during 30 to 60 minutes every 4 to 8 hours or 500 mg/hr (pediatric dose, 10-25 mg/kg/hr).[15,16] The World Health Organization recommends an initial dose of 30 mg/kg, followed by 8 mg/kg/hr continued for at least 24 hours or, if an infusion cannot be used, 30 mg/kg every 4 hours.[17] The infusion may be continued for several days with no adverse effects attributable to the pralidoxime; however, rapid administration can lead to hypertension, vomiting, and a transient reversible neuromuscular blockade.[18] The ideal dose of pralidoxime should be determined by monitoring of the clinical condition of the patient and serial cholinesterase levels; the patient may require higher doses of oxime than are recommended here. The World Health Organization–recommended infusion dose of obidoxime is 4 mg/kg, followed by 0.5 mg/kg/hr; alternatively, intermittent intravenous doses of 4 mg/kg, then 2 mg/kg, every 4 hours are given.[17] Pralidoxime and obidoxime can be administered by intramuscular injection. Indications for oxime therapy include respiratory depression or apnea, fasciculations, seizures, arrhythmias, cardiovascular instability, and use of large amounts of atropine. Oxime therapy can be used whenever the patient requires more than a limited amount of atropine (2-4 mg) to completely reverse the signs and symptoms of intoxication or in any patient who requires repeated doses of atropine. Oxime therapy and atropine are synergistic.

In the past, pralidoxime was used only within the first 24 hours because of aging of the organophosphate-acetylcholinesterase complex, but not all organophosphates behave in a similar manner. Dimethyl and diethyl phosphoryl insecticides react differently at variable rates with acetylcholinesterase and oxime therapy. Many organophosphates are highly lipid soluble and slowly leach out of fat stores for up to 6 weeks, resulting in newly formed complexes with excellent clinical reversal of the cholinesterase inhibition by pralidoxime and by measurements of cholinesterase activity. Pralidoxime can also combine with unbound organophosphates and prevent their subsequent binding to nerve terminals. Even with optimal treatment, seriously intoxicated patients may require long-term supportive care, including ventilator support.[4,16]

Several studies have looked at the efficacy of pralidoxime.[19,20] The results have been mixed and may be due to the variability among different organophosphates. Until this variability is further elucidated, pralidoxime administration in patients with organophosphate toxicity is still recommended.

In conjunction with atropine and the oxime pralidoxime, patients with agitation, seizures, and coma should be treated with adequate doses of a benzodiazepine after the airway has been secured.[4,5,21] Although diazepam is most studied, any parenteral benzodiazepine may be used. The military has classically used diazepam autoinjectors for intramuscular injection, but midazolam is the best intramuscular agent, with lorazepam as an alternative.

Sarin, soman, tabun, and VX are nerve agents that might be used in a terrorist attack. These agents have important differences from the common household or commercial organophosphorus insecticides. These agents tend to age very quickly; tabun (GA) ages in 14 hours, sarin (GB) in 5 hours, soman (GD) in 5 or 6 minutes, and VX in 48 hours. Because of this rapid aging, reversal of nerve agent poisoning with pralidoxime is time sensitive. VX is an oily but highly toxic agent with low volatility. It does not readily vaporize, and because it has a low risk of inhalation, exposure is predominantly transcutaneous. The other agents can be mostly dispersed into the air by explosion or vaporization, resulting in inhalation exposure. These agents do not require the extremely large doses of atropine but do require pralidoxime.[22-24]

New therapies for treatment of organophosphorus poisoning, including the use of *N*-acetylcysteine and exogenous acetylcholinesterase, show promise in research studies.[25,26] When they are added to anticholinergics, NMDA receptor antagonists may decrease organophosphorus compound–induced seizures.[27]

Disposition

Because of the prolonged effects of acetylcholinesterase inhibition, most patients with significant exposures require hospital admission. On occasion, a person with chronic exposure, depressed cholinesterase levels, and mild visual or gastrointestinal symptoms may be observed on an outpatient basis; however, some patients, particularly those exposed to fenthion, initially present with signs and symptoms of mild exposure and progress to severe, life-threatening toxicity over time.[28] If plasma cholinesterase levels are

available, they may be useful for treatment and disposition decisions. Asymptomatic or minimally symptomatic patients with normal or minimally depressed levels may be discharged after 4 to 6 hours with close outpatient follow-up to ensure that progressive toxicity does not occur. Patients who arrive with known severely depressed levels (usually associated with significant symptoms) require admission and close monitoring, usually in a high-intensity care unit. Patients may have rebound toxicity several days after apparently satisfactory response to initial treatment. Rebound toxicity may occur for many reasons, including persistent release of organophosphates from lipid stores.

A secondary syndrome, the intermediate syndrome (IMS), occurs 24 to 96 hours after exposure and consists of proximal muscle weakness specifically of the respiratory muscles. It is believed to be an abnormality at the neuromuscular junction. Patients with IMS present with respiratory failure several days after the acute cholinergic symptoms have resolved and may require several weeks of ventilatory support. It is theorized that this may be a result of inadequate initial oxime treatment or premature discontinuation of oxime therapy.[4,29] Oximes may be beneficial for IMS; however, this is controversial.[30]

Finally, organophosphorus delayed neuropathy has been reported as a different entity. It affects an axonal enzyme, neurotoxic esterase, with a peripheral sensorimotor neuropathy 7 to 21 days after exposure.[4]

CARBAMATE INSECTICIDES

Carbamate insecticides are another class of acetylcholinesterase inhibitors and are differentiated from the organophosphorus compounds by their relatively short duration of toxic effects. Carbamates inhibit acetylcholinesterase for minutes to 48 hours, and the carbamate-cholinesterase binding is reversible. Although the clinical picture of acute carbamate poisoning may be identical to that of organophosphate poisoning, the toxic effects are limited in duration, and patients may require only decontamination, supportive care, and treatment with adequate doses of atropine. Although the duration is limited, patients may become just as ill and require assisted ventilation and seizure therapy. The use of pralidoxime is controversial in carbamate poisoning; an animal study suggests that pralidoxime administration may produce greater toxicity in cases of carbaryl (Sevin) poisoning.[31] Nevertheless, if doubt exists as to whether a severe poisoning is due to a carbamate or organophosphate, pralidoxime should be administered.

CHLORINATED HYDROCARBON INSECTICIDES

DDT, the prototype of chlorinated hydrocarbon insecticides (sometimes referred to as organochlorine insecticides), was first used extensively during World War II for control of typhus and malaria and widely used in the United States as a general insecticide after the war. Because of the effectiveness of DDT, many other chlorinated hydrocarbon insecticides were developed and used extensively in agricultural, commercial, and residential pest control. Although these insecticides were effective, their widespread use, long half-life, and persistence had negative ecologic repercussions. Many of these insecticides have been targeted as persistent organic pollutants by international agencies, leading to their restricted use.[32]

Although chlorinated hydrocarbon insecticides are no longer used in the United States for agricultural use, γ-hexachlorobenzene, better known as lindane (Kwell), is still used as a topical medicinal agent for the treatment of head lice and scabies. As a result, lindane is probably the most common cause of toxicity from an organochlorine compound in the United States. Given its toxicity, lindane is no longer a first-line agent for the treatment of scabies.[33] In 2001, California issued a ban on the use and sale of lindane, and other states are considering a ban on lindane.[32]

Principles of Disease

Chlorinated hydrocarbon pesticides are highly lipid soluble. They are readily absorbed through dermal, respiratory, and gastrointestinal routes. Dermal and gastrointestinal exposures account for most clinical poisonings, including inappropriate external use of lindane or other compounds and the occasional accidental oral administration of lindane. Because they are so lipid soluble, these compounds are stored in fatty tissues, and repeated small exposures result in accumulation and eventual clinical toxicity.

Chlorinated hydrocarbon insecticides primarily affect axonal membranes, resulting in neuronal irritability and excitation. Toxicity occurs in central and peripheral neurons. Some of the organochlorines can inhibit the chloride channel of γ-aminobutyric acid (GABA) receptors, leading to decreased inhibition of the central nervous system. Chlorinated hydrocarbons induce hepatic microsomal enzymes and produce hepatic tumors in some animals. This potential carcinogenicity is the basis for human health concerns, but it is only theoretic. Chlorinated hydrocarbon insecticides, including chlorinated hydrocarbon solvents, may sensitize the myocardium to circulating catecholamines and increase susceptibility to ventricular dysrhythmias, such as tachycardia and fibrillation.

Clinical Features

Signs and Symptoms

The primary clinical picture of acute or cumulative toxicity from chlorinated hydrocarbon pesticides is related to their neurotoxicity. Premonitory peripheral signs and symptoms, such as tremor or paresthesias, may be absent, and the first sign of toxicity may be seizure activity.[34] Additional signs include confusion, combativeness, and muscle twitching. Untreated, continued muscle activity can lead to hyperthermia, metabolic acidosis, and rhabdomyolysis with secondary acute tubular necrosis. Because many of these agents are halogenated, ventricular dysrhythmias may occur from catecholamine sensitization and direct myocardial toxic effects. Immediate hepatotoxicity is unlikely without secondary hyperthermia or other metabolic complications. Long-term exposure may result in neuropsychiatric symptoms.[35] Diagnosis may be difficult in chlorinated hydrocarbon pesticide exposure because the patient may be unable to provide a history. Nonhospital personnel are often in the best position to obtain information on pesticide availability and the situation surrounding the exposure. Another clue is the solvent odor and oily feel of the hydrocarbon solvent containing the highly lipid-soluble chlorinated hydrocarbon pesticides.

Diagnostic Strategies

Diagnosis should be confirmed by history or by investigation at the site of the exposure to establish the offending agent with certainty. No specific tests are readily available to confirm the diagnosis of chlorinated hydrocarbon pesticide poisoning. Some reference laboratories can measure fat and plasma levels, but results are difficult to interpret and seldom available during the acute phase of toxicity. Ancillary laboratory and other studies should be based on the clinical condition, complications, and consideration of alternative diagnoses on an individual basis.

Differential Considerations

The differential diagnosis includes virtually every condition that produces seizures. The specific diagnosis depends on obtaining the history of significant acute or chronic chlorinated hydrocarbon pesticide exposure.

Management and Disposition

Skin decontamination with soap and water may reduce toxicity in acute dermal exposure. High lipid solubility results in rapid absorption, and gastrointestinal decontamination is not of benefit. Elimination of some chlorinated hydrocarbon insecticides can be increased, and repeated doses of cholestyramine (4 g orally every 8 hours) given during a mass exposure of chlordecone (a chlorinated hydrocarbon insecticide) enhanced the fecal elimination of this compound.[35-37]

The primary objective is seizure control, best accomplished with short-acting benzodiazepines or barbiturates. Recurrent seizures or status epilepticus may require high-dose barbiturates and paralyzing agents (e.g., pancuronium or vecuronium) to prevent secondary morbidity from continuous motor activity in prolonged seizures. The seizure activity is usually self-limited, lasting only 1 or 2 days even in severe cases.[34,36,38]

Continuous cardiac monitoring during the acute phase is indicated because of the potential for myocardial sensitization. Ventricular dysrhythmias are most likely to occur during seizure activity because of the high circulating catecholamine levels and other metabolic abnormalities present during seizures. Dysrhythmias should be treated with beta-adrenergic antagonists, such as propranolol, metoprolol, or esmolol, to reduce the effect of catecholamines on the myocardium.

Additional treatment should focus on the complications of prolonged seizure activity, such as rapid external cooling measures for hyperthermia. Metabolic acidosis is almost always transient and resolves spontaneously without treatment. Rhabdomyolysis and myoglobinuria should be anticipated. Because of their high lipid solubility, chlorinated hydrocarbon pesticides are distributed largely in tissues and are not amenable to hemoperfusion or dialysis.

Patients who have acute or cumulative chlorinated hydrocarbon pesticide toxicity require hospitalization until their seizures are controlled, complications have resolved, and they have returned to their neurologic baselines, usually within 1 or 2 days. Severe complications, such as renal failure from rhabdomyolysis, may prolong the clinical course.

SUBSTITUTED PHENOLS

The substituted phenols include dinitrophenol (DNP), pentachlorophenol, and dinitrocresol. These compounds have been used since the 1930s as insecticides, termiticides, herbicides, and wood preservatives. They are currently used in agricultural, commercial, and residential applications, including over-the-counter preparations for home gardeners. Substituted phenols such as DNP are abused as weight reduction agents and occasionally in illegitimate weight reduction operations.[39]

Principles of Disease

Substituted phenols are readily absorbed through the skin and gastrointestinal tract, and aerosols may be absorbed through the respiratory tract. There is some potential for cumulative toxicity with repeated exposures, but much less than with the organophosphorus and chlorinated hydrocarbon pesticides.

Substituted phenols produce their toxicity by uncoupling cellular oxidative phosphorylation; this leads to inefficient production of high-energy phosphate substrates and increased cellular use of oxygen, glucose, and water, with subsequent excess heat production. These compounds are commonly used during the summer when the external heat predisposes users to increased toxicity.[40] In addition, nitro-substituted phenols may produce methemoglobinemia.

Clinical Features

Patients with substituted phenol toxicity present hypermetabolic and hyperthermic, tachycardic, tachypneic, and profusely diaphoretic. They may also have a relative hypovolemia from excessive insensible fluid losses through sweating and metabolic consumption. Loss of energy production in the brain results in neurologic changes ranging from confusion to seizures and coma. Renal and hepatic injury is common, as is rhabdomyolysis with myoglobinuria. Because phenols are corrosive, patients with dermal exposures often have irritation or chemical burns, and some substituted phenols, such as DNP, produce a characteristic yellow staining of the skin or mucous membranes at the site of absorption. This same staining can be found throughout the internal organs at autopsy.

Cataracts are a complication of long-term exposure. This condition was common in patients who used substituted phenols as part of a weight reduction regimen and was partially responsible for the banning of this substance. The cataracts regress spontaneously after exposure is discontinued.

Diagnostic Strategies

Laboratory evaluation of patients with substituted phenol toxicity is aimed at identification of deficiency of aerobic metabolic substrates, including oxygen, glucose, and water. A complete blood count may reveal hemoconcentration and a nonspecific leukocytosis. Electrolyte abnormalities depend on the duration and severity of symptoms, environmental factors, and complications or underlying disease states. Arterial blood gas measurements show varying degrees of acidosis, depending on the extent of anaerobic metabolic activity due to oxidative phosphorylation uncoupling and associated tissue hypoperfusion from dehydration. Serum enzyme determinations document the extent of hepatic, renal, and skeletal muscle injury. The presence of phenolic compounds in the urine of a patient with this clinical picture strongly suggests substituted phenol pesticides as the cause.

Differential Considerations

Acute toxicity from substituted phenol poisoning is difficult to distinguish from environmental heat-related emergencies or toxicity from sympathomimetics or salicylates. Continued evidence of hypermetabolic activity and metabolic acidosis after routine cooling measures, rehydration, and other supportive care should suggest toxin-induced states. Persistent hyperthermia and acidosis in a weight lifter should trigger concern for DNP abuse. The presence of yellow staining virtually clinches the diagnosis.

Management and Disposition

Initial treatment is directed toward control of body temperature; treatment of acidosis; protection of the kidneys, brain, and liver from hyperthermic damage; and provision of the basic substrates for excessive metabolic activity—oxygen, glucose, and water. If the chemical exposure is known or recognized, early skin decontamination is important. Therapy should be directed toward prevention or minimization of the associated complications discussed previously.

Patients with mild toxicity can usually be stabilized after a few hours and discharged from the emergency department. Patients with significant organ system injury or prolonged or recurrent seizures, significant alteration of consciousness, and rhabdomyolysis require admission, usually to the intensive care unit.

CHLOROPHENOXY COMPOUNDS

The chlorophenoxy pesticides were developed in the early 1940s and hailed as a selective herbicide particularly effective against broadleaf weeds. This class of herbicide developed a special notoriety during the Vietnam War as Agent Orange, a defoliant used in aerial spraying, consisting of a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Unfortunately, 2,4,5-T is almost always contaminated with isomers of tetrachlorodibenzodioxin. This concern for dioxin exposure has led to the extensive medical investigations of Vietnam veterans and severe restrictions on the production and use of 2,4,5-T.[41] Because of the relative safety and broadleaf selectivity of 2,4-D, however, most home gardeners have at least one chlorophenoxy compound on a shelf in their garage, and some old cans may contain 2,4,5-T or a mixture of both compounds.

Principles of Disease

Chlorophenoxy compounds may be absorbed through the skin, gastrointestinal tract, and respiratory tract, but almost all significant poisonings are a result of accidental or intentional ingestion. The lipid solubility of these compounds is low, and excretion is fairly rapid, so cumulative toxicity from repeated exposures does not occur.[42]

Although skeletal muscle is the target organ for chlorophenoxy herbicides, the exact mechanism is unknown. Depending on severity, muscle abnormalities may range from generalized muscle weakness to acute rhabdomyolysis. Higher doses may also uncouple oxidative phosphorylation and cause a hypermetabolic state similar to that seen with the substituted phenols.

Clinical Features

Similar to most organic pesticides in an organic solvent, the chlorophenoxy herbicides may produce mild, nonspecific dermal and gastrointestinal irritation with nausea, vomiting, and gastrointestinal distress. Large exposures are likely to cause systemic symptoms ranging from diffuse myotonia and muscle fasciculations progressing to rhabdomyolysis, hyperthermia, and a hypermetabolic state with metabolic acidosis.[43]

Diagnostic Strategies

There are no specific tests for the detection of the chlorophenoxy compounds. Laboratory evaluation should be aimed at evaluation of skeletal muscle injury and its complications. Severely poisoned patients require generalized organ system evaluation, including hepatic and renal function, because of the effects of rhabdomyolysis and hyperthermia.

Differential Considerations

Differential diagnostic possibilities include other causes of acute myopathy. The manifestation of chlorophenoxy compound toxicity is extremely rare, however, and without a definite history or strong suspicion of exposure, other explanations for acute myopathy should be pursued.

Management and Disposition

Treatment consists of initial skin decontamination and basic supportive care. Serious toxic effects develop within 4 to 6 hours after ingestion, and treatment can be directed toward the specific problems of muscle weakness, airway and ventilatory support, and rhabdomyolysis. Treatment of hyperthermia and acidosis has been discussed previously.

Asymptomatic or minimally symptomatic patients may be discharged after 4 to 6 hours of observation. Patients with muscle effects should be admitted for close observation and monitoring of respiratory effort.

BIPYRIDYL COMPOUNDS

The bipyridyl (also called dipyridyl) compounds paraquat and diquat were first investigated in the late 1950s and early 1960s. They are extremely effective contact herbicides that are rapidly inactivated by the surrounding soil in the event of overspray. Paraquat is activated when it is exposed to sunlight, which led to its use as the herbicide of choice during aerial spraying of marijuana by the U.S. and Mexican governments. After spraying, however, growers simply would harvest the crops before the plants were exposed to enough sunlight to damage them, resulting in an apparently healthy harvest but one contaminated with paraquat. The burning of marijuana pyrolyzes paraquat into a nontoxic form, a fact that was lost in the warning messages dispensed by the government at that time.[44]

Principles of Disease

Of the two bipyridyl compounds in use, paraquat is the most significant in terms of number of cases and toxic effects. Paraquat use is tightly regulated in the United States but is widespread throughout the world. Diquat is less regulated in the United States and is included in some formulations of herbicides sold for residential use. Paraquat is absorbed through the skin, gastrointestinal tract, and respiratory tract. Almost all fatal exposures have resulted from the ingestion of paraquat, although a few case reports have involved extensive skin contamination. Toxicity has occurred, but no fatal cases have been reported from inhalation of paraquat vapor or aerosols. Diquat is poorly absorbed through intact skin, and most cases of toxicity result from ingestion.[45]

Paraquat's toxic effect is from the production of superoxides created during cyclic oxidation-reduction reactions of the compound in tissues. Lipid peroxidation of cellular membranes seems to be one significant pathway of cellular injury.[46,47]

Paraquat selectively concentrates in the lungs because of an amine uptake mechanism in alveolar cells. In addition, high concentrations of oxygen significantly increase the extent of paraquat-induced injury so that the lungs are the major target organs. The pathophysiologic lesions include direct injury to the alveolar-capillary membrane followed by surfactant loss, adult respiratory distress syndrome, progressive pulmonary fibrosis, and respiratory failure. Paraquat damages other major organ systems by the same cellular membrane effects, including the liver, kidneys, heart, and central nervous system. Diquat has similar effects, with most of its toxicity concentrated in the kidneys rather than in lung tissue.[45]

Clinical Features

Signs and Symptoms

Both agents are extremely corrosive and cause nausea, vomiting, and severe chemical burns of the oropharynx soon after ingestion.

Patients who ingest concentrated paraquat frequently die of esophageal perforation and mediastinitis before development of the characteristic progressive pulmonary injury. Patients with dermal paraquat exposures show significant skin irritation, and ocular exposures may produce severe corneal burns.

The paraquat-induced pulmonary injury usually progresses during 1 to 3 weeks, although the clinical course varies considerably with severity of poisoning, involvement of other organ systems, and underlying medical problems. This is not a factor in the emergency department, and the delayed pulmonary injury is not discussed here. Diquat usually spares the lungs but produces similar toxicity in all other organ systems.[45]

Diagnostic Strategies

Paraquat is measurable in the blood. As long as the time of acute exposure is known, the level serves as an accurate prognostic marker. The assay is not readily available in the United States, and by the time the results are obtained, nothing can be done to change the eventual outcome. There is a qualitative bedside test that uses the reduction of paraquat or diquat in alkalinized urine by sodium dithionite, but the reagent frequently is not available.[43] Studies should evaluate caustic gastrointestinal injury and pulmonary and renal damage.

Differential Considerations

A person with acute paraquat or diquat ingestion is likely to present with an acute corrosive injury; the differential diagnosis should encompass all corrosive agents. Successful therapeutic intervention for paraquat toxicity is extremely time dependent, and patient outcome depends on the history. Any patient who has evidence of pulmonary or other organ injury from paraquat exposure is probably already beyond recovery.

Management and Disposition

There are no studies comparing various treatment strategies, but the key to successful treatment of an acute paraquat exposure probably depends on early decontamination measures to limit absorption. There are no effective treatments once clinical effects are seen. Thorough skin cleansing is obvious and straightforward in dermal exposures. Careful gastric lavage and administration of activated charcoal may be lifesaving and should be undertaken in consultation with a poison center or a medical toxicologist. These treatments may be hazardous in the context of a corrosive ingestion. Early endoscopy and surgical intervention may be necessary if there is evidence of esophageal perforation and mediastinitis. Although fuller's earth and bentonite are recommended as adsorbents in paraquat ingestions, activated charcoal is much more readily available in the United States and has equal if not greater efficacy.

Oxygen treatment can theoretically exacerbate paraquat toxicity by the production of superoxides. Therefore, oxygen should be used only as minimally necessary in these cases.

Although it is controversial, many experts recommend rapid initiation of charcoal hemoperfusion to rapidly lower plasma paraquat levels and to limit pulmonary and other organ system uptake of paraquat. Many also recommend serial and combined hemoperfusion and hemodialysis, particularly during the first 24 hours after exposure.

Cyclophosphamides in combination with corticosteroids have also been investigated as a means to attenuate paraquat toxicity.[48,49] Whereas the results have been mixed, this therapy has been recommended by some experts in the setting of significant paraquat toxicity.

There are other suggested treatment adjuncts, such as *N*-acetylcysteine, nitric oxide, deferoxamine, and cytoprotective agents such as amifostine, but no single therapy has proved consistently successful.[50]

Patients with any significant dermal paraquat exposure and all patients with ingested paraquat require hospitalization and consideration of enhanced elimination therapy. These patients should be observed and treated expectantly until paraquat levels, if available, are reported to be nonexistent or nontoxic.

PYRETHRINS AND PYRETHROIDS

Pyrethrins are naturally occurring insecticides of the yellow *Chrysanthemum cinerariifolium* and *Tanacetum cinerariifolium* and are among the oldest known insecticides, first used in the 1800s. Extracts of the dried flowers contain the active compound pyrethrum, which contains six naturally occurring pyrethrins. In addition, numerous synthetic derivatives, pyrethroids, have been produced and have greater chemical stability than the natural pyrethrins. Type II pyrethroids contain a cyano substituent and are among the more toxic formulations of this class. These present a potential danger to humans, but type II pyrethroids are generally less toxic than many of the other classes already discussed and are being used more commonly.

Principles of Disease

Because pyrethrins and pyrethroids are most commonly aerosolized, inhalation is the most likely route of exposure. The patient may not be aware of an exposure because pyrethrin and pyrethroid aerosols are used frequently as automated insect sprays in public areas, such as in airplanes. In these situations, concentrations rarely reach levels likely to produce symptoms in any but the most sensitized patient. Occasional ingestions have been reported, and significant toxicity is possible by this route. Systemic absorption through the dermal route is unlikely, but topical effects are possible. Most pyrethrins and pyrethroids are rapidly metabolized and deactivated in human exposure, so cumulative toxicity is not a problem. Piperonyl butoxide, which is added as an insect "knock-down" agent, may increase the toxicity of the pyrethrum derivatives.

Pyrethrins and pyrethroids have a variety of effects in humans and other mammals.[51,52] Clinically, the naturally occurring pyrethrins can cause sensitization and allergic phenomena, but this does not occur with the synthetic pyrethroids. Both classes are associated with sodium channel blockade, slowing the rate of activation of the sodium channel and extending the time during which the channel is open. In addition, both classes affect GABA receptors, inhibiting chloride channel function. Less significant effects include potentiation of nicotinic cholinergic neurotransmission, enhancement of norepinephrine release, and inhibition of calcium adenosine triphosphatase interference with sodium-calcium exchange across membranes.[51,52]

Clinical Features

Effects are very rare. Allergic manifestations, including potentially life-threatening events, may occur after acute inhalation or dermal exposure. Inhalation exposure often occurs with the use of a pyrethrin-based aerosol in an enclosed, poorly ventilated space. Local effects include lacrimation, rhinitis, rhinorrhea, sneezing, throat irritation, and pharyngeal and laryngeal edema. Lower respiratory effects include cough, shortness of breath, chest pain, and wheezing. Rashes are consistent with a contact or allergic dermatitis, and photosensitivity may contribute to the dermatologic picture. There is potential for allergic cross-reactivity in patients who are allergic to ragweed.

Sodium channel–mediated and GABA-mediated chloride channel effects mediate neurologic signs and symptoms. Facial paresthesias have been reported, and seizures occur with massive ingestions.[51,52] Nonspecific symptoms, such as headache, fatigue, dizziness, and weakness, are also reported.

Diagnostic Strategies

No laboratory tests are available to measure pyrethrins or pyrethroids in a clinical setting.

Differential Considerations

The differential diagnosis of the signs and symptoms of pyrethrin or pyrethroid toxicity includes the usual causes of bronchospasm and seizures and other acute neurologic complications.

Management and Disposition

Decontamination, including removal from a contaminated environment or washing, should be the first step. Definitive treatment is supportive and directed at the respiratory and neurologic complications.

Disposition of a patient with exposure to pyrethrins depends on the severity of the underlying complications. If discharge from the emergency department is anticipated, the patient should be counseled with regard to the possibility of recurrent allergic phenomena on reexposure.

GLYPHOSATE

Glyphosate was introduced as a broad-spectrum nonselective herbicide in 1971. It is the isopropyl ammonium salt of a non–cholinesterase-inhibiting organophosphate herbicide. It is sold mixed with the surfactant polyoxyethylene amine (POEA). Because it is effective on broadleaf weeds and does not undergo photodecomposition, it is popular in the home market, known as Roundup. Newer formulations of residential-use herbicides may contain glyphosate in conjunction with diquat.

Principles of Disease

Glyphosate is poorly absorbed through the skin so that most exposures result from ingestion. The concentrated solution is extremely irritating, and patients may vomit with subsequent aspiration. The concentrated solution is provided as 41% glyphosate in 15% POEA. The directions state that it should be diluted to a 1% glyphosate solution.

Glyphosate is toxic to plants by inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase in the shikimic acid metabolic pathway. After application of glyphosate on the leaves, it is transported to the roots, where the enzyme is active. Humans lack this enzyme and do not have enzyme-related toxicity. Reported toxicity is believed to result largely from the surfactant POEA and may reflect the direct corrosive effect from the amine salt, or it may uncouple oxidative phosphorylation.[53]

Clinical Features

Most ingestions of the dilute solution cause only minimal symptoms, including gastrointestinal distress. Patients ingesting large volumes of dilute solutions or moderate volumes of concentrated solutions complain of sore throat, nausea, abdominal pain, and fever. They may have vomiting, diarrhea, respiratory distress, noncardiogenic pulmonary edema, dysrhythmias, shock, coma, and renal failure. Acidosis reflects poor tissue perfusion and cardiovascular compromise.[53] Negative prognostic indicators include shock, acidosis, and persistent hyperkalemia.[53]

Diagnostic Strategies

The critical element in diagnosis is history of ingestion. Laboratory analysis may demonstrate an anion gap metabolic acidosis, hypoxemia, and hyperkalemia. Elevated transaminases may occur in 30% of ill patients, and signs of renal failure may develop in persistent shock states. The electrocardiogram may show ventricular dysrhythmias and secondary signs of hypoxemia.[53]

Differential Diagnosis

The differential diagnosis includes most corrosive ingestions and causes of shock. The findings of hyperkalemia and metabolic acidosis may suggest hydrofluoric acid ingestions. A normal ionized calcium level may help rule out hydrofluoric acid exposure. Any cause of aspiration should also be considered. The history is the most useful factor in the differential diagnosis.

Management and Disposition

Treatment is supportive. The patient may require positive-pressure ventilation to overcome the noncardiogenic pulmonary edema. POEA may also be a direct cardiac depressant; inotropic agents can be useful. Hyperkalemia should be treated in the usual manner with fluids, medications to shift potassium into the cell (e.g., bicarbonate, calcium, and beta-adrenergic agonists), and Kayexalate. If there is an indication of significant corrosive ingestion, early endoscopy with placement of stent, high-dose steroids, and laparotomy may be considered.

Asymptomatic patients with small ingestions of dilute substances may be observed for 6 hours and discharged. Patients with complaints consistent with corrosive ingestions should be admitted and have a gastrointestinal evaluation. Patients with pulmonary complaints require admission and intensive supportive care.

DEET

N,*N*-Diethyl-*m*-toluamide or *N*,*N*-diethyl-3-methylbenzamide (DEET) is not a pesticide but an insect repellent. It is the most widely used chemical insect repellent in the United States. DEET was developed by scientists at the U.S. Department of Agriculture in 1946, patented by the U.S. Army soon thereafter, and released to the general public in 1957.[54] With the prevalence of Lyme disease and other concerning arthropod-borne diseases, the use of DEET has greatly increased. Formulations containing DEET range from 5 to 100%. The U.S. Army routinely used 75% solutions until 1987 but now uses a 35% time-release, polymer-based formulation. The American Academy of Pediatrics recommends 30% as the maximum concentration for use in infants and children and does not recommend use of DEET in infants younger than 2 months.[55]

Principles of Disease

DEET is lipophilic and can be absorbed through the skin. Skin absorption and toxicity increase with repeated applications, increased ambient temperatures, sweating, and abraded, thin skin. Ingestion may lead to toxicity.[56] DEET primarily affects the central nervous system. Its mechanism of action is unknown. It may sensitize the skin and cause allergic reactions.

Clinical Features

Prolonged skin contact may lead to contact dermatitis, and prolonged contact with high concentrations has led to skin blisters. Patients who have ingested DEET or have repeated skin applications in a hot enclosed environment that enhances absorption have developed liver function test abnormalities and neurologic findings, including encephalopathy, seizures, movement disorders, and coma.[56] Most exposures to DEET result in no or minimal toxicity and should not preclude its use in susceptible populations in which significant arthropod-borne diseases are prevalent.[57]

Diagnostic Strategies

Exposure history is central to the diagnosis. Although DEET can be detected in urine, most laboratories are not able to do this testing during the acute toxicity phase. An electroencephalogram may be useful in a patient with coma or encephalopathy and seizures.

Differential Diagnosis

The differential diagnosis includes conditions that may cause encephalopathy, seizures, and movement disorders. Such conditions include drug intoxication, infectious causes, drug interactions, and structural defects.

Management and Disposition

Treatment is supportive. If DEET exposure is suspected, the skin should be thoroughly decontaminated. Oils or lipophilic agents should be avoided because they enhance skin absorption. After DEET ingestion, milk products and oil-containing foods should be avoided until the gastrointestinal tract has eliminated the offending agent. Seizures should be treated with benzodiazepines.

Asymptomatic patients who have ingested DEET-containing repellents should be observed for 4 to 6 hours. Patients who have neurologic symptoms should be admitted and observed.

KEY CONCEPTS

- All patients exposed to cholinesterase inhibitors should have skin decontamination. Health care personnel need to be protected during this process.
- Morbidity in cholinesterase inhibitor exposure results from early airway compromise secondary to copious secretions, status epilepticus, and late respiratory failure.
- Cholinesterase inhibitor exposure may include bradycardia or tachycardia, hypertension or hypotension, and miosis or mydriasis.
- The clinical endpoint for atropine administration is drying of airway secretions.
- Pralidoxime should be given to all organophosphorus-poisoned patients who require atropine regardless of time since exposure.
- With chlorinated hydrocarbon exposures, skin decontamination with protection of personnel is indicated.
- In chlorinated hydrocarbon exposures, supportive care, temperature control, and seizure control are important and catecholamine administration is avoided.
- Rapid cooling and glucose are the two most important therapies in substituted phenol toxicity.
- Diagnosis of chlorophenoxy compound toxicity depends on a history of accidental or deliberate ingestion.
- Rapid gastrointestinal decontamination is indicated in paraquat and diquat ingestions despite the corrosive injury.
- The predominant form of pyrethrin and pyrethroid toxicity is allergic.
- Small ingestions of dilute glyphosate solutions are gastrointestinal irritants. Large or concentrated ingestions may cause acidosis, hyperkalemia, and noncardiogenic pulmonary edema.
- DEET should not be applied over abraded or raw skin.
- DEET applications to children should be restricted to 30% solutions, should not be used under occlusive clothing, and should be washed off completely between applications.

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The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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