

HIGHLIGHTS

Derived from living systems

Bacillus thuringiensis is the most important live agent

Generally of low-order toxicity

Poison control center advice can help avoid potentially harmful treatment

SIGNS & SYMPTOMS

Highly variable based on specific agents

Several cause GI irritation

Nicotine may have serious CNS effects

Nicotine and sabadilla may have cardiovascular effects

TREATMENT

Specific to the agent

Skin, eye, GI decontamination may be indicated

Nicotine and sabadilla may require aggressive support

Avermectin COMMERCIAL PRODUCTS

avermectin B1 (Abamectin)

emamectin benzoate (salt of avermectin)

ivermectin

CHAPTER 8

Biologicals and Insecticides of Biological Origin

This chapter concerns several widely used insecticidal products of natural origin, and also certain agents usually identified as biological control agents. This latter group includes many living control agents, though only the bacterial agent *Bacillus thuringiensis* will be discussed in detail, as it is one of the most widely used. Other agents, such as parasitic wasps and insects, are so host specific they pose little or no risk to man.

Many of the pesticides in this chapter, with the notable exception of nicotine, are relatively less toxic to mammals than to insects. Consequently, there may be no findings of toxicity following ingestion of these compounds. While clinicians should always consider calling their regional poison control center (1-800-222-1222) for advice on any poisoning, it may be of particular value in the case of some of these biological pesticides, where no treatment is warranted and poison control center advice can help avoid potentially harmful treatments.

Agents are presented in alphabetical order.

AVERMECTIN

Source and Products

Avermectin and related products are synthetically derived from the toxin of the soil bacterium *Streptomyces avermitilis*. They are used for control of mites, fire ants (ant bait stations) and other insects. **Ivermectin** is used as an antihelminth and a miticide.

Toxicology and Signs and Symptoms of Poisoning

Avermectins work by stimulating the gamma amino butyric acid (GABA) receptor, thereby inhibiting nerve conduction to nerves and muscles. The result is insect paralysis and death within a few days. Mammalian GABA receptors reportedly have a much lower affinity for avermectins than insect GABA receptors.¹ Reports of acute toxicity are uncommon in the medical literature. Clinical manifestations appear to most prominently involve the nervous, GI and respiratory systems. Patients may initially present with nausea, vomiting, salivation, diarrhea and dizziness. More severe manifestations may include aspiration pneumonia, respiratory failure, hypotension and coma.^{1,2,3} Rhabdomyolysis has also been reported.² One case study of 19 patients demonstrated a dose/response relationship, with the most severe toxicity occurring in patients who ingested in the range of 67 mg/kg to 227 mg/kg. One exception was a patient who ingested 15 mg/kg and had severe toxic symptoms. Most patients who ingested less than 40 mg/kg exhibited either mild or no toxicity.²

Treatment

1. Provide supportive treatment as there is no antidotal therapy.

2. Remove skin contamination with soap and water. Remove eye contamination by flushing the eyes with clean water or saline.
3. If ingested, consider gastrointestinal decontamination as outlined in **Chapter 3, General Principles**.

AZADIRACTIN

Source and Products

This compound is a biologically obtained insecticide derived from the neem tree (*Azadirachta indica*). It is an insect growth regulator that interferes with the molting hormone ecdysone.

Toxicology and Signs and Symptoms of Poisoning

Azadirachtin causes severe dermal and gastrointestinal irritation. Central nervous system stimulation and depression have been seen. This agent is primarily used and manufactured in India, so little use or exposures are expected in the United States.

Treatment

1. Wash skin thoroughly with soap and water if skin has been exposed.
2. Do not use gastric emptying or catharsis because of severe gastrointestinal irritation. Do not use activated charcoal when there is severe GI irritation because of potential need for gastrointestinal endoscopy.

BACILLUS THURINGIENSIS

Source and Products

Several strains of *Bacillus thuringiensis* are pathogenic to some insects. The bacterial organisms are cultured and then harvested in spore form for use as insecticide. Production methods vary widely. Proteinaceous and nucleotide-like toxins generated by the vegetative forms (which infect insects) are responsible for the insecticidal effect. The spores are formulated as wettable powders, flowable concentrates and granules for application to field crops and for control of mosquitoes and black flies.

Toxicology and Signs and Symptoms of Poisoning

The varieties of *Bacillus thuringiensis* used commercially survive when injected into mice, and at least one of the purified insecticidal toxins is toxic to mice. Infections of humans have been extremely rare. A single case report of ingestion by volunteers of *Bacillus thuringiensis* var. *galleriae* resulted in fever and gastrointestinal symptoms. However, this specific agent is not registered as a pesticide. *B. thuringiensis* products are exempt from tolerances on raw agricultural commodities in the United States. Neither irritative nor sensitizing effects have been reported in workers preparing and applying commercial products. A single case of corneal ulcer caused by a splash of *B. thuringiensis* suspension into the eye has been reported.⁴

Bacillus thuringiensis

COMMERCIAL PRODUCTS

Several varieties are available:

kurstaki

israelensis

aizawai

morrisoni

tenebrionis

Treatment

1. Remove skin contamination with soap and water. Remove eye contamination by copious flushing of the eyes with clean water or saline. If irritation persists, or if there is any indication of infection, refer patient for further treatment.
2. Observe a patient who has ingested a *B. thuringiensis* product for manifestations of bacterial gastroenteritis: abdominal cramps, vomiting and diarrhea. The illness is likely to be self limited if it occurs at all. The patient should be treated symptomatically and fluid support provided as appropriate.

EUGENOL

Source and Products

This compound is derived from clove oil, which is found in the dried flower bud of *Eugenia caryophyllata*. It is used as an insect attractant. It is also used in numerous dental products, which accounts for some of the reports of toxicity.⁵

Toxicology

Eugenol is similar in its clinical effects to phenol in terms of its caustic properties. Although it works as an anesthetic, in large doses, it can cause burns to epithelial surfaces.⁶ Sloughing of mucous membranes occurred as an allergic reaction to a small dose applied topically in the mouth.⁵ Gastric mucosal lesions have been reported in animals, but no lesions were seen on endoscopy after clove oil ingestion.⁷ Large doses may result in coma, metabolic acidosis, seizures, liver dysfunction and disseminated intravascular coagulation.^{8,9,10} Large ingestions can be particularly toxic to children. The mechanism of liver toxicity appears to be similar to that of acetaminophen poisoning, in which eugenol is metabolized by the cytochrome-p450 system to produce a toxicologically active quinone metabolite and a resultant glutathione depletion.^{11,12}

Treatment

1. Provide supportive treatment as necessary as there is no antidote.
2. Consider gastrointestinal decontamination as outlined in **Chapter 3, General Principles**, for ingestions. If mucosal burns are present, consider endoscopy to look for other ulcerations.

There is one report of the use of n-acetylcysteine, using the same dose prescribed for acetaminophen ingestion. It is of note that the patient's hepatic transaminase levels began to decrease sharply after initiating NAC therapy.⁹ Without further study, it is difficult to recommend this as routine treatment.

GIBBERELIC ACID (GIBBERELLIN, GA₃)

Source and Products

Gibberellic acid is not a pesticide, but it is commonly used in agricultural production as a growth-promoting agent. It is a metabolic product of a cultured fungus, formulated in tablets, granules and liquid concentrates for application to soil beneath growing plants and trees.

Toxicology

Experimental animals tolerate large oral doses of **gibberellic acid** without apparent adverse effect. No human poisonings have been reported. Sensitization has not been reported, and irritant effects are not remarkable.

Treatment

1. Provide supportive treatment for any toxic effects in humans, as there is no known antidote.
2. Wash contamination from skin with soap and water. Flush contamination from eyes with clean water or saline. If irritation occurs, refer patient for further medical treatment.
3. For significant ingestion, consider gastrointestinal decontamination as outlined in **Chapter 3, General Principles**, although that may not be necessary. Poison control centers may be helpful to guide whether any therapy is indicated based on the ingestion.

NICOTINE

Source and Products

Nicotine is an alkaloid contained in the leaves of many species of plants, but is usually obtained commercially from the tobacco plant (*Nicotiana tabacum*). A 95% solution of the free alkaloid in organic solvent has been marketed in the past as a greenhouse fumigant. Another product used for the same purpose is a 40% aqueous solution of nicotine sulfate. Significant volatilization of nicotine occurs from both products. Commercial nicotine insecticides have long been known as Black Leaf 40. This formulation was discontinued in 1992, although old preparations of nicotine insecticides may still be found on occasion.¹³ The last remaining registered nicotine product will be discontinued as of 2013 by request of the registrant.¹⁴ Today, most nicotine poisonings are the result of ingestion of tobacco products and ingestion and/or incorrect use of nicotine replacement products such as nicotine gum and transdermal patches.^{15,16} However, ingestions from old pesticide products may still occur.¹⁷

Toxicology

Nicotine alkaloid is efficiently absorbed by the gut, lung and skin. Extensive biotransformation occurs in the liver, with 70%-75% occurring as a first-pass effect.¹⁸ Both the liver and kidney participate in the formation and excretion of multiple end-products, which are excreted within a few hours. Estimates of the half-life of nicotine range from about 1 hour in smokers to as much as 2 hours in non-smokers.^{19,20}

Toxic action is complex. At low doses, autonomic ganglia are stimulated. At higher doses, blockade of autonomic ganglia and skeletal muscle neuromuscular junctions and direct effects on the central nervous system occur. Paralysis and vascular collapse are prominent features of acute poisoning, but death is often due to respiratory paralysis, which may ensue promptly after the first symptoms of poisoning.^{14,17} Nicotine is not an inhibitor of cholinesterase enzyme.

Nicotine HIGHLIGHTS

Efficiently absorbed by gut,
lung, skin

CNS impacts

Respiratory impacts

SIGNS & SYMPTOMS

Salivation, sweating,
dizziness, nausea, vomiting,
diarrhea

Possible burning in mouth/
throat, agitation, confusion,
headache, abdominal pain

Cardiovascular symptoms at
high dosage/exposure

TREATMENT

Decontaminate eyes, skin

Maintain airway

Limit GI absorption

IV atropine if indicated

Control seizures

Signs and Symptoms of Poisoning

Early and prominent symptoms of poisoning include salivation, sweating, dizziness, nausea, vomiting and diarrhea. Burning sensations in the mouth and throat, agitation, confusion, headache and abdominal pain are reported. Cardiovascular symptoms are prominent with high dosages of exposure. In severe poisoning, cardiovascular collapse is manifested by bradycardia or other arrhythmias and hypotensive shock.^{13,17,21,22,23} Patients may have dyspnea, then respiratory failure and unconsciousness.^{13,21,22,23} In some cases, hypertension and tachycardia may precede hypotension and bradycardia.^{21,22} Seizures may also occur.^{13,17,22} In one case of ingestion of a large dose of nicotine alkaloid pesticide, the patient developed asystole within 2 minutes. He later developed seizures and refractory hypotension.¹³ A child developed seizures, respiratory depression and hypoxic encephalopathy after ingesting a nicotine-containing pesticide.¹⁷

If symptoms of poisoning appear during exposure to an airborne nicotine insecticide, the person should be removed from the contaminated environment immediately and any skin areas that may be contaminated should be washed. The victim should then be transported to the nearest treatment facility. Although mild poisoning may resolve without treatment, it is often difficult to predict the ultimate severity of poisoning at the onset.

Confirmation of Poisoning

Urine, plasma and salivary content of the metabolite cotinine can be used to confirm absorption of nicotine. However, these studies generally need to be sent to a reference lab and are not clinically useful in acute toxicity. Treatment should be based on clinical presentation and findings. If necessary, lab confirmation can be done at a later date.

Treatment of Nicotine Toxicosis

1. If liquid or aerosol spray has come in contact with skin, wash the area thoroughly with soap and water. If eyes have been contaminated, flush them thoroughly with clean water or saline. If irritation persists, refer patient for specialized medical treatment.
2. If there is any indication of loss of respiratory drive, maintain pulmonary ventilation by mechanical means. Toxic effects of nicotine other than respiratory depression are usually survivable. Maintaining adequate gas exchange is therefore of paramount importance.
3. If a nicotine-containing product has been ingested recently, take immediate steps to limit gastrointestinal absorption. If the patient is fully alert, immediately administer activated charcoal orally as outlined in the **Chapter 3, General Principles**. This is probably the best initial step in management. Since most patients who ingest nicotine have significant vomiting, activated charcoal is not always necessary. Do not administer cathartics or syrup of ipecac.
4. Manage patients with severe poisoning in the intensive care environment, preferably with toxicology consultation if available. Monitor cardiac status by electrocardiography and measure blood pressure frequently. Cardiopulmonary resuscitation may be necessary. Vascular collapse may require administration of vasopressors. Infusions of electrolyte solutions, plasma and/or blood may also be required to combat shock.

5. Treat excessive parasympathetic stimulation, such as severe hypersecretion (especially salivation and diarrhea) or bradycardia, with intravenous atropine sulfate. There is no specific antidote for nicotine poisoning.

Dosage of Atropine Sulfate

- **Adults and children over 12 years: 0.5-1.0 mg slow IV, repeated every 5 minutes if necessary.**
- **Children under 12 years: 0.02 mg/kg body weight, slow IV, repeated every 5 minutes if necessary. (Minimum dose of 0.1 mg.)**

6. Control seizures as outlined in **Chapter 3, General Principles**.

ROTENONE

Source and Products

Although this natural substance is present in a number of plants, the source of most rotenone used in the United States is the dried derris root imported from Central and South America. It is formulated as dusts, powders and sprays (less than 5% active ingredient) for use in gardens and on food crops. Many products contain piperonyl butoxide as a synergist, and other pesticides are included in some commercial products. Rotenone degrades rapidly in the environment. Emulsions of rotenone are applied to lakes and ponds to kill fish.

Toxicology and Manifestations of Poisoning

Although **rotenone** is toxic to the nervous systems of insects, fish and birds, commercial rotenone products have presented little hazard to man over many decades. Neither fatalities nor systemic poisonings in humans have been reported in relation to ordinary use. However, there is one report of a fatality in a child who ingested a product called Gallocide, which contains rotenone and etheral oils, including clove oil (eugenol). She developed a gradual loss of consciousness over 2 hours and died of respiratory arrest.²⁴

There have been some reports of toxic symptoms following occupational exposure. Eye irritation is the most common. In addition, numbness of oral mucous membranes has been reported in workers who got dust from the powdered derris root in their mouths. Dermatitis, respiratory tract irritation, headaches and peripheral neuropathy have also been reported.²⁵

When rotenone has been injected into animals, tremors, vomiting, incoordination, seizures and respiratory arrest have been observed. These effects have not been reported in occupationally exposed humans.

Treatment of Rotenone Toxicosis

1. Provide supportive treatment, as there is no specific antidote.

2. Remove skin contamination by washing with soap and water. Remove eye contamination by flushing the eye thoroughly with clean water or saline. Wash out any dust in the mouth. If irritation persists, refer for further medical treatment.
3. If a large amount of a rotenone-containing product has been swallowed and retained, consider gastric decontamination as outlined in **Chapter 3, General Principles**.

SABADILLA (VERATRUM ALKALOID)

Source and Products

Sabadilla consists of the powdered ripe seeds of a South American lily. Its only remaining registered use in the United States is for agricultural application to citrus fruits, avocados and mangos.²⁶ Insecticidal alkaloids are those of the *Veratrum* plant. The concentration of alkaloids in commercial sabadilla is usually less than 0.5%. Little or no sabadilla is used in the United States today, but it is probably used in other countries. Although poisoning by medicinal *Veratrum* preparations may have occurred in the remote past, systemic poisoning by sabadilla preparations used as insecticides has been very rare. Much of the toxic encounters with *Veratrum* alkaloid occur from the inadvertent ingestion of the *Veratrum* plant or a related plant from the genus *Zigadenus*.^{27,28}

Toxicology

Sabadilla dust is very irritating to the upper respiratory tract, causing sneezing, and is also irritating to the skin. *Veratrum* alkaloids are apparently absorbed across the skin and gut, and probably by the lung as well. *Veratrum* alkaloids have a digitalis-like action on the heart muscles (impaired conduction and arrhythmia).^{27,29,30}

Signs and Symptoms of Poisoning

The prominent symptoms of *Veratrum* alkaloid poisoning are severe nausea and vomiting, increased salivation and mental status changes. Cardiovascular effects may be severe, including hypotension and bradycardia. Other arrhythmias or A-V block may occur in large ingestions. These symptoms often resolve within 24 hours.^{27,29,30}

Treatment of Sabadilla Toxicosis

1. Wash contaminated skin thoroughly with soap and water. Flush eyes, if affected, with copious amounts of clean water or saline. If skin or eye irritation persists, refer patient for further medical treatment.
2. Consider gastric decontamination as outlined in **Chapter 3, General Principles**.
3. If there is a suspicion that significant amounts of sabadilla alkaloids have been absorbed, monitor cardiac activity for arrhythmia and conduction defects with an ECG. Place patient with severe toxicity in intensive care. Treat bradycardia with atropine.^{29,30}

Dosage of Atropine Sulfate

- **Adults and children over 12 years: 0.5-1.0 mg slow IV, repeated every 5 minutes, if necessary.**
- **Children under 12 years: 0.02 mg/kg body weight, slow IV, repeated every 5 minutes, if necessary. (Minimum dose of 0.1 mg.)**

Spinosyns COMMERCIAL PRODUCTS

Spinosad (a mixture of Spinosyn A and Spinosyn D)

SPINOSYNS

Source and Products

Spinosad is a biologically based synthetic pesticide that is used to control a variety of insects including fleas, mites, fire ants, caterpillars, fruit flies and leaf beetle larvae. It has recently been approved to treat head lice in humans.³¹ The spinosyns are derived from the rare soil-dwelling actinomycete bacterium called *Saccharopolyspora spinosa*.

Toxicology and Manifestations of Poisoning

Spinosad must be ingested by the target pest to control it. It causes rapid excitation of the insect's nervous system and is relatively fast acting. Spinosyns interfere with nicotinic function and also disrupt GABA function in central nervous system neurons; however, they do not bind to the receptor sites.³² Spinosad has low mammalian oral toxicity (LD₅₀ rat is >3,000 mg/kg).³³ Similar to fipronil, spinosyns have a much higher affinity for insects than for mammals. There have not been reports of human toxicity in the medical literature.

Treatment

1. Provide supportive treatment should toxic effects occur in humans, as there is no known antidote.
2. Wash contamination from skin with soap and water. Flush contamination from eyes with clean water or saline. If irritation occurs, refer for further medical treatment.
3. For significant ingestion, consider gastrointestinal decontamination as outlined in **Chapter 3, General Principles**, although that may not be necessary. Poison control centers may be helpful to guide whether any therapy is indicated based on the ingestion.

STREPTOMYCIN

Source and Products

Streptomycin sulfate and nitrate are used as pesticides for the control of a variety of commercially important bacterial plant pathogens. Streptomycin is an antibiotic derived from the growth of *Streptomyces griseus*.

Toxicology

Streptomycin shares a toxic profile with the aminoglycoside antibiotics commonly used to treat human diseases. Its major modes of toxicity are nephrotoxicity and ototoxicity. Fortunately, it is poorly absorbed from the gastrointestinal tract, so systemic toxicity is unlikely with ingestion. It may cause some minor nausea and GI upset.

Treatment

If a large amount has been ingested and 1 hour or less has passed, consider gastric decontamination as outlined in **Chapter 3, General Principles**.

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