CHAPTER 7

Biologicals and Insecticides of Biological Origin

This chapter covers several widely-used insecticidal products of natural origin, as well as certain agents often identified as biological control agents. Of the many living control agents, only the bacterial agent *Bacillus thuringiensis* will be discussed in detail, since it is one of the most widely used. Many other agents, such as parasitic wasps and insects, are so host-specific that they pose little or no risk to human health. The agents are discussed in this chapter in alphabetic order.

AZADIRACHTIN

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

Toxicology

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; little use or exposures are expected in the United States.

Treatment

1. Skin decontamination. If skin exposure occurs, the skin should be thoroughly washed with soap and water.

2. Gastrointestinal decontamination. Due to the severe gastrointestinal irritation, gastric emptying and catharsis are not indicated. Consideration should be given to administration of activated charcoal as outlined in Chapter 2.

HIGHLIGHTS

- Derived from living systems
- *Bacillus thuringensis* is the most important live agent
- Generally of low order toxicity

Signs and Symptoms:

- Highly variable based on specific agents
- Several cause gastrointestinal irritation
- Nicotine and rotenone may have serious CNS effects
- Nicotine and sabadilla may have cardiovascular effects

Treatment:

- Specific to the agent
- Skin, eye, and GI decontamination may be indicated
- Nicotine, rotenone, and sabadilla require aggressive support

Commercial Products

azadirachtin
- Align
- Azatin
- Bollwhip
- Neemazad
- Neemazal
- Neemix
- Turplex

Bacillus thuringiensis
- Variety *aizawai*:
  - Agree
  - Design
  - Mattch
  - XenTari
- Variety *israelensis*:
  - Aquabac
  - Bactimos
  - Gnatrol
  - Skeetal
  - Teknar
  - Vectobac
  - Vectocide
- Variety *kurstaki*:
  - Bactospeine
  - Bactur
  - Dipel
  - Futura
  - Sok-Bt
  - Thuricide
  - Tribactur
- Variety *morrisoni*
- Variety *tenebrionis*:
  - Novodor

eugenol

gibberellic acid (GA_3)
- Activol
- Berelex
- Cekugib
- Gibberellin
- Gibrel
- Grocel
- Pro-Gibb
- Pro-Gibb Plus
- Regulex

nicotine
- Black Leaf 40
- Nico Soap

pyrethrins

rotenone
- Chem-Fish
- Noxfire
- Noxfish
- Nusyn-Foxfish
- Prenfish

(Continued on the next page)

BACILLUS THURINGIENSIS

Several strains of *Bacillus thuringiensis* are pathogenic to some insects. The bacterial organisms are cultured, 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

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 agent is not registered as a pesticide. *B. thuringiensis* products are exempt from tolerance on raw agricultural commodities in the United States. Neither irritative nor sensitizing effects have been reported in workers preparing and applying commercial products.

Treatment

1. Skin decontamination. Skin contamination should be removed with soap and water. Eye contamination should be flushed from the eyes with clean water or saline. If irritation persists, or if there is any indication of infection, treatment by a physician should be obtained.

A single case of corneal ulcer caused by a splash of *B. thuringiensis* suspension into the eye was successfully treated by subconjunctival injection of gentamicin (20 mg) and cefazolin (25 mg).[1]

2. Gastrointestinal decontamination. If a *B. thuringiensis* product has been ingested, the patient should be observed 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

This compound is derived from clove oil. It is used as an insect attractant.

Toxicology

Eugenol is similar in its clinical effects to phenol. Although it works as an anesthetic, in large doses it can cause burns to epithelial surfaces.[2] Sloughing of mucous membranes has occurred as an allergic reaction to a small dose applied topically in the mouth.[3] Gastric mucosal lesions have been reported in animals, but no lesions were seen on endoscopy after clove oil ingestion.[4] Large doses may result in coma and liver dysfunction.[5]

Treatment

Treatment is primarily supportive as there is no antidote. If mucosal burns are present, consider endoscopy to look for other ulcerations.

GIBBERELLIC ACID (Gibberellin, GA_3)

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 without apparent adverse effect. No human poisonings have been reported. Sensitization has not been reported, and irritant effects are not remarkable.

Treatment

1. Skin decontamination. Wash contamination from skin with soap and water. Flush contamination from eyes with clean water or saline. If irritation occurs, obtain medical treatment.

2. Gastrointestinal decontamination. If gibberellic acid has been swallowed, there is no reason to expect adverse effects.

NICOTINE

Nicotine is an alkaloid contained in the leaves of many species of plants, but is usually obtained commercially from tobacco. A 14% preparation of the free alkaloid is marketed as a greenhouse fumigant. Significant volatilization of nicotine occurs. Commercial nicotine insecticides have long been known as Black Leaf 40. This formulation was discontinued in 1992. Other currently

Commercial Products

(Continued)

- Rotacide
- Rotenone Solution FK-11
- Sypren-Fish

sabadilla

streptomycin
- Agri-Mycin 17
- Paushamycin, Tech.
- Plantomycin

*Discontinued in the U.S.

available formulations include dusts formulated with naphthalene and dried blood used to repel dogs and rabbits. Be aware of Green Tobacco Syndrome from dermal absorption. Very little nicotine insecticide is currently used in the United States, although old preparations of nicotine insecticides may still be found on occasion.[6] Today, most nicotine poisonings are the result of ingestion of tobacco products and incorrect use of nicotine skin patches.

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.[7] 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 one hour in smokers to as much as two hours in non-smokers.[8,9]

Toxic action is complex. At low doses, autonomic ganglia are stimulated. Higher doses result in blockade of autonomic ganglia and skeletal muscle neuromuscular junctions, and direct effects on the central nervous system. 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. Nicotine is not an inhibitor of the cholinesterase enzyme.

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. If dosage has been high, vascular collapse with hypotension, bradycardia or other arrythmias, dyspnea then respiratory failure, and unconsciousness may ensue promptly.[6,10,11,12] In some cases, hypertension and tachycardia may precede hypotension and bradycardia, with the latter two signs leading to shock.[11,12] Seizures may also occur.[6,11] In one case of ingestion of a large dose of nicotine alkaloid pesticide, the patient developed asystole within two minutes. He later developed seizures and refractory hypotension.[6]

Confirmation of Poisoning

Urine content of the metabolite cotinine can be used to confirm absorption of nicotine.

Treatment

1. Skin decontamination. 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, obtain specialized medical treatment.

If symptoms of poisoning appear during exposure to an airborne nicotine insecticide, remove the person from the contaminated environment immediately, wash any skin areas that may be contaminated, then transport the victim 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.

2. Pulmonary ventilation. If there is any indication of loss of respiratory drive, maintain pulmonary ventilation by mechanical means, using supplemental oxygen if available, or mouth-to-mouth or mouth-to-nose methods if necessary. Toxic effects of nicotine other than respiratory depression are usually survivable. The importance of maintaining adequate gas exchange is therefore paramount.

3. Gastrointestinal decontamination. If a nicotine-containing product has been ingested recently, immediate steps must be taken to limit gastrointestinal absorption. If the patient is fully alert, immediate oral administration of activated charcoal as outlined in Chapter 2 is probably the best initial step in management. Repeated administration of activated charcoal at half or more the initial dosage every 2-4 hours may be beneficial. Since diarrhea is often a part of this poisoning, it is usually not necessary or appropriate to administer a cathartic. Do not administer syrup of ipecac.

4. Cardiac monitoring. Monitor cardiac status by electrocardiography, and measure blood pressure frequently. **Cardiopulmonary resuscitation may be necessary.** Vascular collapse may require administration of norepinephrine and/or dopamine. Consult package inserts for dosages and routes of administration. Infusions of electrolyte solutions, plasma, and/or blood may also be required to combat shock.

5. Atropine sulfate. There is no specific antidote for nicotine poisoning. Severe hypersecretion (especially salivation and diarrhea) or bradycardia may be treated with intravenous atropine sulfate. See dosage on next page.

Dosage of Atropine Sulfate:

- *Adults and children over 12 years:* 0.4-0.5 mg slowly IV, repeated every 5 minutes if necessary.
- *Children under 12 years:* 0.01 mg/kg body weight, slowly IV, repeated every 5 minutes if necessary. There is a minimum dose of 0.1 mg.

6. Convulsions should be controlled as outlined in Chapter 2. If the patient survives for four hours, complete recovery is likely.

PYRETHRUM AND PYRETHRINS

Pyrethrum is the oleoresin extract of dried chrysanthemum flowers. The extract contains about 50% active insecticidal ingredients known as pyrethrins. The ketoalcoholic esters of chrysanthemic and pyrethroic acids are known as pyrethrins, cinerins, and jasmolins. These strongly lipophilic esters rapidly penetrate many insects and paralyze their nervous systems. Both crude pyrethrum extract and purified pyrethrins are contained in various commercial products, commonly dissolved in petroleum distillates. Some are packaged in pressurized containers ("bug-bombs"), usually in combination with the synergists piperonyl butoxide and n-octyl bicycloheptene dicarboximide. The synergists retard enzymatic degradation of pyrethrins. Some commercial products also contain organophosphate or carbamate insecticides. These are included because the rapid paralytic effect of pyrethrins on insects ("quick knockdown") is not always lethal.

Pyrethrum and pyrethrin products are used mainly for indoor pest control. They are not sufficiently stable in light and heat to remain as active residues on crops. The synthetic insecticides known as pyrethroids (chemically similar to pyrethrins) do have the stability needed for agricultural applications. Pyrethroids are discussed separately in Chapter 8.

Toxicology

Crude pyrethrum is a dermal and respiratory allergen, probably due mainly to non-insecticidal ingredients. Contact dermatitis and allergic respiratory reactions (rhinitis and asthma) have occurred following exposures.[13,14] Single cases exhibiting anaphylactic[15] and pneumonitic manifestations[16] have also been reported. The refined pyrethrins are probably less allergenic, but appear to retain some irritant and/or sensitizing properties.

Pyrethrins are absorbed across the gut and pulmonary membrane, but only slightly across intact skin. They are very effectively hydrolyzed to inert products by mammalian liver enzymes. This rapid degradation combined with relatively

poor bioavailability probably accounts in large part for their relatively low mammalian toxicity. Dogs fed extraordinary doses exhibit tremor, ataxia, labored breathing, and salivation. Similar neurotoxicity rarely, if ever, has been observed in humans, even in individuals who have used pyrethrins for body lice control (extensive contact) or pyrethrum as an anthelmintic (ingestion).

In cases of human exposure to commercial products, the possible role of other toxicants in the products should be kept in mind. The synergists piperonyl butoxide and n-octyl bicycloheptene dicarboximide have low toxic potential in humans, but organophosphates or carbamates included in the product may have significant toxicity. Pyrethrins themselves do not inhibit cholinesterase enzyme.

Confirmation of Poisoning

There are at present no practical tests for pyrethrin metabolites or pyrethrin effects on human enzymes or tissues that can be used to confirm absorption.

Treatment

1. Antihistamines are effective in controlling most allergic reactions. Severe asthmatic reactions, particularly in predisposed persons, may require administration of inhaled B_2-agonists and/or systemic corticosteroids. Inhalation exposure should be carefully avoided in the future.

2. Anaphylaxis-type reactions may require sub-cutaneous epinephrine, epinepherine, and respiratory support.[15]

3. Contact dermatitis may require extended administration of topical corticosteroid preparations. This should be done under the supervision of a physician. Future contact with the allergen must be avoided.

4. Eye contamination should be removed by flushing the eye with large amounts of clean water or saline. Specialized ophthalmologic care should be obtained if irritation persists.

5. Other toxic manifestations caused by other ingredients must be treated according to their respective toxic actions, independent of pyrethrin-related effects.

6. Gastrointestinal decontamination. Even though most ingestions of pyrethrin products present little risk, if a large amount of pyrethrin-containing material has been ingested and the patient is seen within one hour, consider gastric emptying. If the patient is seen later, or if gastric emptying is performed, consider administration of activated charcoal as described in Chapter 2.

ROTENONE

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 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

Although rotenone is toxic to the nervous systems of insects, fish, and birds, commercial rotenone products have presented little hazard to humans over many decades. Neither fatalities nor systemic poisonings 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. She developed a gradual loss of consciousness over two hours and died of respiratory arrest.[17]

Numbness of oral mucous membranes has been reported in workers who got dust from the powdered derris root in their mouths. Dermatitis and respiratory tract irritation have also been reported in occupationally exposed persons.

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

Treatment

1. Skin decontamination. Skin contamination should be removed by washing with soap and water. Eye contamination should be removed by flushing the eye thoroughly with clean water or saline. Dust in the mouth should be washed out. If irritation persists, medical treatment should be obtained.

2. Gastrointestinal decontamination. If a large amount of a rotenone-containing product has been swallowed and retained and the patient is seen within an hour of exposure, consideration should be given to gastric emptying. Whether or not gastric emptying is performed, consider use of activated charcoal as outlined in Chapter 2.

3. Respiratory support should be used as necessary if mental status changes and/or respiratory depression occurs.

SABADILLA (Veratrum alkaloid)

Sabadilla consists of the powdered ripe seeds of a South American lily. It is used as dust, with lime or sulfur, or dissolved in kerosene, mainly to kill ectoparasites on domestic animals and humans. Insecticidal alkaloids are those of the veratrum type. 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 some is probably used in other countries. Most toxic encounters with veratrum alkaloid occur from the inadvertent ingestion of the plant.[18]

Toxicology

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

Although poisoning by medicinal veratrum preparations may have occurred in the past, systemic poisoning by sabadilla preparations used as insecticides has been very rare. The prominent symptoms of veratrum alkaloid poisoning are severe nausea and vomiting, followed by hypotension and bradycardia. Other arrythmias or A-V block may occur.[18,19]

Treatment

1. Skin decontamination. Contaminated skin should be washed thoroughly with soap and water. If eyes are affected, they should be flushed with copious amounts of clean water or saline. If skin or eye irritation persists, medical treatment should be obtained.

2. Gastrointestinal decontamination. If a large amount of sabadilla pesticide product has been ingested in the past hour and retained, consider gastric emptying. This may be followed by administration of charcoal. If only a small amount of sabadilla pesticide has been ingested and retained, or if treatment is delayed, and if the patient remains fully alert, immediate oral administration of activated charcoal probably represents reasonable management, as outlined in Chapter 2.

3. Cardiac monitoring. If there is a suspicion that significant amounts of sabadilla alkaloids have been absorbed, ECG monitoring of cardiac activity for arrhythmia and conduction defects is appropriate. Bradycardia may be treated with atropine.[18,19] See dosage on next page.

Dosage of Atropine Sulfate:

- *Adults and children over 12 years:* 0.4-0.5 mg slowly IV, repeated every 5 minutes if necessary.
- *Children under 12 years:* 0.01 mg/kg body weight, slowly IV, repeated every 5 minutes if necessary. (There is a minimum dose of 0.1 mg).

STREPTOMYCIN

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

This antibiotic 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.

Treatment

If a large amount of streptomycin has been ingested within one hour of the patient's receiving care, gastric emptying should be considered. Administration of activated charcoal, as outlined in Chapter 2, should be considered.

References

1. Samples JR and Buettner H. Corneal ulcer caused by a biological insecticide (Bacillus thuringiensis). *Am J Ophthalmol* 1983;95:258.
2. Isaacs G. Permanent local anesthesia and anhydrosis after clove oil spillage. *Lancet* 1983;1:882.
3. Barkin ME, Boyd JP, and Cohen S. Acute allergic reaction to eugenol. *Oral Surg Oral Med Oral Pathol* 1984;57:441-2.
4. Lane BW, Ellenhorn MJ, Hulbert TV, et al. Clove oil ingestion in an infant. *Hum Exp Toxicol* 1991;10:291-4.
5. Hartnoll G, Moore D, and Douek D. Near fatal ingestion of oil of cloves. *Arch Dis Child* 1993;69:392-3.
6. Lavoie FW and Harris TM. Fatal nicotine ingestion. *J Emerg Med* 1991;9:133-6.
7. Svensson CK. Clinical pharmacokinetics of nicotine. *Clin Pharm* 1987;12:30-40.

8. Kyerematen MS, Damiano MD, Dvorchik BH, et al. Smoking-induced changes in nicotine disposition: Application of a new HPLC assay for nicotine and its metabolites. *Clin Pharmacol Ther* 1982;32:769-80.

9. Feyerabend C, Ings RMJ, and Russell MAH. Nicotine pharmacokinetics and its application to intake from smoking. *Br J Clin Pharmacol* 1985;19:239-47.

10. Woolf A, Burkhart K, Caraccio T, et al. Self-poisoning among adults using multiple transdermal nicotine patches. *J Toxicol Clin Toxicol* 1996;34:691-8.

11. Sanchez P, Ducasse JL, Lapeyre-Mestre M, et al. Nicotine poisoning as a cause of cardiac arrest? (letter). *J Toxicol Clin Toxicol* 1996;34:475-6.

12. Malizia E, Andreucci G, Alfani F, et al. Acute intoxication with nicotine alkaloids and cannabinoids in children from ingestion of cigarettes. *Hum Toxicol* 1983;2:315-6.

13. Moretto A. Indoor spraying with the pyrethroid insecticide lambda-cyhalothrin: Effects on spraymen and inhabitants of sprayed houses. *Bull World Health Organ* 1991; 69:591-4.

14. Newton JG and Breslin ABX. Asthmatic reactions to a commonly used aerosol insect killer. *Med J Aust* 1983; 1:378-80.

15. Culver CA, Malina JJ, and Talbert RL. Probable anaphylactoid reaction to a pyrethrin pediculocide shampoo. *Clin Pharm* 1988;7:846-9.

16. Carlson JE and Villaveces JW. Hypersensitivity pneumonitis due to pyrethrum. *JAMA* 1977;237:1718-9.

17. DeWilde AR. A case of fatal rotenone poisoning in a child. *J Forensic Sci* 1986;31(4):1492-8.

18. Jaffe AM, Gephardt D, and Courtemanche L. Poisoning due to ingestion of veratrum viride (false hellebore). *J Emerg Med* 1990;8:161-7.

19. Quatrehomme G, Bertrand F, Chauvet C, et al. Intoxication from veratrum album. *Hum Exp Toxicol* 1993;12:111-5.