Pyrethrins
HIGHLIGHTS

Strongly lipophilic

Crude pyrethrum is a dermal & respiratory allergen

Easily absorbed by GI tract & pulmonary membranes

Relatively low mammalian toxicity

SIGNS & SYMPTOMS

Contact dermatitis

Rhinitis, asthma

TREATMENT

Antihistamines

Epinephrine for anaphylaxis as required

Topical corticosteroid for contact dermatitis

Flush eyes as necessary

Consider gastric emptying or charcoal adsorption

CHAPTER 4

Pyrethrins and Pyrethroids

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. 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) have the stability needed for agricultural applications. Pyrethroids are discussed separately below.

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.[1,2] Single cases exhibiting anaphylactic[3] and pneumonitic manifestations[4] have also been reported. Pulmonary symptoms may be due to inhalation of the hydrocarbon vehicle(s) of the insecticides. The refined pyrethrins are probably less allergenic but appear to retain some irritant and/or sensitizing properties.

Pyrethrins are absorbed across the gastrointestinal tract and pulmonary membranes, 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 has been rarely observed in humans, even in individuals who have had extensive contact from using pyrethrins for body lice control or have ingested pyrethrum as an anthelmintic.

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, which is further discussed in **Chapter 19, *Miscellaneous Pesticides, Solvents and Adjuvants*.** However, the hydrocarbon vehicle(s) may have significant toxicity. Pyrethrins themselves do not inhibit the cholinesterase enzymes.

Confirmation of Poisoning

No practical tests for pyrethrin metabolites or pyrethrin effects on human enzymes or tissues are currently available.

Treatment of Pyrethrin or Pyrethrum Toxicosis

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

2. For anaphylaxis-type reactions, use subcutaneous epinephrine, epinephrine and respiratory support as necessary.[3]

3. In cases of contact dermatitis, administer topical corticosteroid preparations for an extended period, as necessary, under the supervision of a physician. Future contact with the allergen must be avoided.

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

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

6. 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 1 hour, consider gastric emptying. If seen later, or if gastric emptying is performed, consider administration of activated charcoal as described in **Chapter 3, *General Principles***.

PYRETHROIDS

These modern synthetic insecticides are similar chemically to natural pyrethrins, but pyrethroids are modified to increase stability in the natural environment. They are now widely used in agriculture, in homes and gardens, and for treatment of ectoparasitic disease. There has been increasing use of these agents as use of organophosphate pesticides becomes more restricted.[5]

Toxicology

Although certain **pyrethroids** exhibit striking neurotoxicity in laboratory animals when administered by intravenous injection and some are toxic by the oral route, systemic toxicity by inhalation and dermal absorption is low. While limited absorption may account for the low toxicity of some pyrethroids, rapid biodegradation by mammalian liver enzymes (ester hydrolysis and oxidation) is probably the major factor responsible for this phenomenon.[6,7] Neonatal rats have been demonstrated to have decreased ability to metabolize and excrete pyrethroids. The LD_{50} for weanling rats with deltamethrin has been reported at 12 mg/kg, while the adult LD_{50} is about 80 mg/kg. At these doses, the brain levels of deltamethrin at death are equivalent in both weanling and adult rats.[8] Most pyrethroid metabolites are promptly excreted, at least in part, by the kidneys.

Multiple mechanisms and targets have been evaluated for mammalian toxicity. At concentrations as low as 10^{-10} M in *in vitro* systems, pyrethroids alter sodium and chloride channels and result in norepinephrine release. At concentrations around 10^{-7} M, membrane depolarization and apoptosis occur, as well as other cellular effects. In laboratory animal studies, this results in a state of hyperexcitability at lower expo-

Pyrethroids
HIGHLIGHTS

Low systemic toxicity via inhalation and dermal route

Sites of action: sodium & chloride channels; GABA, nicotinic acetylcholine, peripheral benzodiazepine receptors

Type I (*e.g.,* permethrin) usually do not contain a cyano group

Type II (*e.g.,* cypermethrin, fenvalerate) always contain a cyano group

Type II acute poisonings are generally more severe

SIGNS & SYMPTOMS

Type I: fine tremor, reflex hyperexcitability

Type II: severe salivation, hyperexcitability, choreoathetosis

May include dizziness, headache, fatigue, vomiting, diarrhea

Stinging, burning, itching, tingling, numb skin may be reported

Severe cases: pulmonary edema, seizures, coma

TREATMENT

Decontaminate skin, eyes

Consider GI decontamination

Treat seizures as necessary

sures, followed by depolarization, conduction block and cell death at very high levels of exposure.[7] In addition to the calcium and sodium channel sites of action, multiple other sites described include GABA receptors (for Type II effects, see following), nicotinic acetylcholine receptors and peripheral benzodiazepine receptors. They have also been shown to alter mitochondrial electron transport.[9]

These discrete effects at differing levels and the relative resistance of mammals to these agents explain the typical syndromes of human poisoning. However, the possibility of neuronal death with prenatal exposure or with repeated dosing in adults has been raised.[7] The potential decreased ability of the fetus to metabolize these agents could result in higher levels in the developing brain, with resulting neurotoxicity.

Pyrethroids have been divided into two types based on clinical findings with overdosing. Type I pyrethroids, such as **permethrin**, usually do not contain a cyano group, while most Type II pyrethroids, such as **cypermethrin** and **fenvalerate**, always do.[10] Both of these types show marked stimulus of catecholamine release from the adrenals with overdosing. This release of epinephrine and norepinephrine results in marked sympathetic symptoms.

There have been recent reports of illnesses due to these agents. A report of 466 episodes of illnesses and injuries related to total release foggers notes that eight of the ten most commonly reported active ingredients in these episodes are pyrethroid compounds, representing 86% of all reported episodes.[11] In these cases, 18% were reported as moderate severity and 2% were classified as high severity.

Signs and Symptoms of Poisoning

Type II acute poisonings are generally more severe than Type I.[10] Type I poisoning has been described as characterized by fine tremor and reflex hyperexcitability. Type II poisoning has typically shown severe salivation, hyperexcitability and choreoathetosis. Other signs and symptoms of toxicity include abnormal facial sensation, dizziness, headache, fatigue, vomiting, diarrhea and irritability to sound and touch. In more severe cases, pulmonary edema, muscle fasiculations, seizures and coma can develop. A large ingestion (200 to 500 mL) of concentrated formulations may cause coma and seizures within 20 minutes. Initial symptoms following ingestion include gastrointestinal events (*i.e.,* abdominal pain, vomiting and diarrhea) generally within 10 to 60 minutes. Of 573 cases reviewed in China, 51 included disturbed consciousness and 34 included seizures. Of those 85 symptomatic cases, only five were from occupational exposure.[12]

A report of illnesses in 27 farmworkers and 4 emergency responders was related to pesticide drift of the pyrethroid **cyfluthrin**.[13] In this episode, the most commonly reported symptoms were headache (96%), nausea (89%), eye irritation (70%), muscle weakness (70%), anxiety (67%) and shortness of breath (64%).[13]

Apart from central nervous system toxicity, some pyrethroids do cause distressing paresthesias when liquid or volatilized materials contact human skin. These symptoms are more common with exposure to the Type II pyrethroids than the Type 1.[6] Sensations are described as stinging, burning, itching and tingling, progressing to numbness.[12,14,15] The skin of the face seems to be most commonly affected, but the hands, forearms and neck are sometimes involved. Sweating, exposure to sun or heat and application of water enhance the disagreeable sensations. Sometimes the paresthetic effect is noted within minutes of exposure, but a 1-2 hour delay in appearance of symptoms is more common.[14,16] Sensations rarely persist more than 24 hours.[7] Little or no inflammatory reaction is apparent where the paresthesias are reported; the effect is presumed to result from pyrethroid contact with sensory nerve endings in the skin. The paresthetic reaction is not allergic in nature, though sensitization and allergic responses have been

reported as an independent phenomenon with pyrethroid exposure. However, allergic responses are less likely with pyrethroids than with pyrethrins. Race, skin type and disposition to allergic disease do not affect the likelihood or severity of the reaction.

Persons treated with permethrin for lice or flea infestations sometimes experience itching and burning at the site of application, but this is chiefly an exacerbation of sensations caused by the parasites themselves and is not typical of the paresthetic reaction described above.

Pyrethroids are not cholinesterase inhibitors. However, there have been some cases in which pyrethroid poisoning has been misdiagnosed as organophosphate poisoning, due to similar presenting signs.[7,12] There are also reports of mixed poisoning where the initial diagnosis of organophosphate poisoning had to be reconsidered when the response to atropine was more prompt and complete than expected.[16]

Confirmation of Poisoning

Pyrethroid metabolites can be measured in the urine; however, this is not routinely available for the acutely poisoned patient. The following metabolites have been detected in occupationally exposed workers: cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid, cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid, 3-phenoxybenzoic acid and 4-fluoro-3-phenoxybenzoic acid.[17]

Treatment of Pyrethroid Toxicosis

Decontaminate the skin promptly with soap and water as outlined in **Chapter 3, *General Principles***. If irritant or paresthetic effects occur, obtain treatment by a physician. Because volatilization of pyrethroids apparently accounts for paresthesia affecting the face, strenuous measures should be taken (ventilation, protective face mask and hood) to avoid vapor contact with the face and eyes. Vitamin E oil preparations (dl-alpha tocopheryl acetate) are uniquely effective in preventing and stopping the paresthetic reaction.[14,18] They are safe for application to the skin under field conditions. Corn oil is somewhat effective, but possible side effects with continued use make it less suitable. Vaseline is less effective than corn oil, and zinc oxide actually worsens the reaction.

Treat eye contamination immediately by prolonged flushing with copious amounts of clean water or saline. Some pyrethroid compounds can be very corrosive to the eyes, so extraordinary measures should be taken to avoid eye contamination. If irritation persists, professional ophthalmologic care should be obtained.

If large amounts of pyrethroids, especially the cyano-pyrethroids, have been ingested and the patient is seen soon after exposure, consider gastrointestinal decontamination as outlined in **Chapter 3**. Based on observations in laboratory animals[6] and humans,[12] large ingestions of allethrin, cismethrin, fluvalinate, fenvalerate or deltamethrin would be the most likely to generate neurotoxic manifestations.

If only small amounts of pyrethroid have been ingested, or if treatment has been delayed, administer activated charcoal and a cathartic orally as this probably represents optimal management. Do not give cathartic if patient has diarrhea or an ileus.

Pyrethroids
COMMERCIAL PRODUCTS

This list includes the names of several pyrethroids that are not currently in commercial production. These are included because they may be marketed in the future, if not in the United States, then possibly in other countries.

allethrin (Pynamin)

barthrin*

bioallethrin (D-trans)

bioresmethrin*

biopermethrin*

cismethrin*

cyfluthrin (Baythroid)

cypermethrin (Ammo, Barricade, CCN52, Cymbush, Cymperator, Cynoff, Cyperkill, Demon, Folcord, KafilSuper, NRDC 149, Polytrin, Siperin, Ripcord, Flectron, Ustadd, Cyrux, many others)

deltamethrin (DeltaDust, DeltaGard, Suspend, Deltex, Decis)

dimethrin

fenothrin*

fenpropanate*

fenpropathrin (Danitol, Herald, Meothrin, Rody)

fenvalerate (Belmark, Sumicidin, Fenkill)

flucythrinate (Cybolt, Payoff, Fluent)

fluvalinate*

furethrin*

continued next page

Pyrethroids
COMMERCIAL PRODUCTS
continued

permethrin (Ambush, Dragnet, Eksmin, Kafil, Permasect, Perthrine, Pounce, Pramex, Outflank, Talcord and others)

phthalthrin*

resmethrin (Benzofuroline, Chrysron, Pynosect)

tetramethrin (Neopynamin)

tralomethrin (Tralex, SAGA)

Nix and Elimite − permethrin creams applied to control human ectoparasites

**Not registered in the U.S.*

Treat seizures as outlined in **Chapter 3**. Several drugs are effective in relieving the pyrethroid neurotoxic manifestations observed in deliberately poisoned laboratory animals, but none has been tested in human poisonings. Therefore, neither efficacy nor safety under these circumstances is known. Furthermore, moderate neurotoxic symptoms and signs are likely to resolve spontaneously.

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