Chapter 39

Pyrethrins and Pyrethroids

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INTRODUCTION

Pyrethrins are the insecticidal compounds obtained from the flowers of the plant *Tanacetum cinerariaefolium*, also called *Chrysanthemum cinerariaefolium* or *Pyrethrum cinerariaefolium*. Pyrethrum comes from extracts from the flowers that contain the active pyrethrin compounds (Proudfoot, 2005). The use of pyrethrum in insecticide preparations dates back to Persia, about 400 BC. Pyrethroids are synthetic analogs of pyrethrins. Because of stability problems with the natural pyrethrins, these insecticides were replaced by the more stable organophosphate and organochlorine insecticides developed after World War II (Valentine, 1990). As a result of the toxicity and environmental contamination associated with the organophosphate and organochlorine insecticides, interest in the use of pyrethrins and pyrethroids reemerged in the 1970s. Pyrethrin and pyrethroid insecticides are effective against a variety of insect pests on companion animals and livestock, and are used on farms, in the home and garden and have many public health applications because of the safety associated with these compounds. The pyrethroids are considerably safer than the organochlorines. The neonicotinoids were developed to replace the pyrethrins.

BACKGROUND

There are six compounds that comprise the natural pyrethrins: pyrethrin I and II, jasmolin I and II, and cinerin I and II. Synthetic pyrethroids have been developed because the natural pyrethrins tend to break down quickly when exposed to air, light and heat. The synthetic pyrethroids can be classified as first and second generation. First-generation pyrethroids are esters of chrysanthemic acid and an alcohol, having a furan ring and terminal side chain moieties. Second-generation pyrethrins have 3-phenoxybenzyl alcohols derivatives in the alcohol moiety and have had some of the terminal side chain moieties replaced with a dichlorovinyl or dibromovinyl substitute and aromatic rings. The addition of the alpha-cyano group to the 3-phenoxybenzyl alcohol group in the second-generation pyrethroids has increased the insecticidal potency and stability of these compounds.

Pyrethrins cause hyperexcitability with very little cytotoxicity. The molecular targets of the pyrethrins and pyrethroids are similar in mammals and insects and include voltage-gated sodium, chloride and calcium channels, GABA-gated chloride channels, nicotinic receptors, membrane depolarization and intercellular gap junctions (Forshaw and Ray, 1990; Song and Narahashi, 1996a). Mammals are less susceptible to pyrethrin and pyrethroid toxicoses than insects primarily because they have a faster metabolic clearance, higher body temperatures and a lower affinity for the pyrethrins/pyrethroids (Song and Narahashi, 1996b; Gammon et al., 2012).

PHARMACOKINETICS/TOXICOKINETICS

Determination of the toxicity of pyrethroids in vivo is difficult because they have low water solubility, easily partition into lipids and will bind to plastics and glass. The reported toxicity of this class of insecticides has high variability.

Most pyrethrin and pyrethroid products are applied dermally in animals, but because of grooming, there can be oral and inhalation exposures, too (Anadón et al., 2013). Less than 2% of topically applied pyrethrin and pyrethroid insecticides are absorbed dermally (Wollen et al., 1992). One study confirmed that absorption of cypermethrin across human skin is minimal and peak excretion rates after dermal application were not observed until 12−36 h after dosing. Pyrethrins may be sequestered in the skin and slowly released into the systemic circulation (He et al., 1989). Oral or inhalation exposure results in faster systemic exposure (Anadon et al., 1996, 2013).

Approximately 40%−60% of an orally ingested dose is absorbed. When cypermethrin was administered orally to six adult male volunteers, oral absorption ranged from

Veterinary Toxicology. DOI: http://dx.doi.org/10.1016/B978-0-12-811410-0.00039-8

27% to 57% of the administered dose and peak excretion rates were measured in the urine between 8 and 24 h after dosing. When adult males were exposed to cyfluthrin at 160 μg/m^3, 93% of the metabolites were excreted within the first 24 h with peak excretion rates ranging from 0.5 to 3 h.

Pyrethroids are lipophilic and will distribute to tissues with high lipid content such as fat and nervous tissue in addition to liver, kidney and milk. Kim et al. (2008) described the pharmacokinetics and tissue distribution of deltamethrin in adult rats following oral or intravenous administration. Utilizing a physiologically based toxicokinetic model, GI absorption of deltamethrin was rapid, but bioavailability was low. Deltamethrin in blood was largely present in plasma. A very small proportion of the absorbed doses reached or remained in the brain. Fat, skin and muscle ultimately accumulated large amounts of this highly lipophilic insecticide.

Pyrethroids and pyrethrins are rapidly hydrolyzed in the gastrointestinal tract. Once absorbed these compounds are metabolized by mixed function oxidases and esterases. Metabolism of the pyrethroids results in water-soluble metabolites. Metabolism includes hydrolysis of the central ester bond, oxidation at several sites and conjugation with glycine, sulfate, glucuronide, or glucosides. Cleavage of the ester bond results in substantial reduction in toxicity. The presence of the alpha-cyano group, as in type II pyrethroids, will decrease the rate of hydrolysis of the ester bond. Cleavage of the alpha-cyano group results in rapid conversion of the cyano group to thiocyanate. For the detailed metabolism of different pyrethroids, readers are referred to Gammon et al. (2012).

Pyrethroids are eliminated by first order kinetics and most of the dose is eliminated in the first 12−24 h after absorption. The pyrethroids are rapidly metabolized to inactive metabolites, which are primarily excreted in the urine (Fig. 39.1).

MECHANISM OF ACTION

Pyrethroids primarily affect the sodium channel of cells, but chloride and calcium channels are also affected (Gammon et al., 2012; Soderlund, 2012; Meijer et al., 2014). Pyrethrins and pyrethroids slow the opening and closing of the sodium channels, resulting in excitation of the cell (Marban et al., 1989; Conley and Brammar, 1999). The increase of sodium in the sodium channels results in a cell that is in a stable, hyperexcitable state. The duration of the sodium action potential is much longer for type II pyrethroids than for type I. Type I pyrethroids result in primarily repetitive charges with membrane depolarization predominating in type II pyrethroids. Paresthesia results from the direct action of pyrethroids on sensory nerve endings, causing repetitive firing of these fibers. Less than 1% of sodium channels must be modified by pyrethroids to produce neurological signs. High concentrations of type II pyrethroids may also act on GABA-gated chloride channels (Bloomquist et al., 1986).

Pyrethrins also affect the voltage-dependent chloride channels. These channels are found in the brain, nerve, muscle, and salivary gland, and control cell excitability. There are many different functional types of chloride channels in contrast to sodium channels. Most pyrethroid-sensitive channels belong to the Maxi chloride channel class. Maxi channels are activated by depolarization, have high conductance, are calcium independent and are activated by protein kinase C phosphorylation. Pyrethroids cause a decrease in the Maxi chloride channel current, which increases excitability of the cell just as the action of pyrethroids on the sodium channel.

The decreased sensitivity of mammals to this class of compounds compared to insects is due to several factors. Pyrethroids bind more strongly with the sodium channel at low temperatures than at high temperatures. Insects' ambient temperature is approximately 25°C compared to mammals at 37°C. Mammalian sodium channels are at least 1000 times less sensitive to pyrethroids than insect sodium channels. Mammalian sodium channels recover much more quickly from depolarization than do insect sodium channels and are much more likely to detoxify pyrethroids before they reach their target site than are insects.

Pyrethroids cause a phenomenon in insects called "knockdown" (Narahashi, 1985). Knockdown is caused by inhibiting the cell but does not cause a lethal effect. This is caused from the ability of the sodium channels to retain many of the normal functions, such as selectivity for sodium ions and conductance after exposure to pyrethroids. After exposure to moderate doses of pyrethroids, cells function in a new state of hyperexcitability. If the level of sodium in the ion channel does not exceed the ability of the sodium pump to remove it, the cell continues to function normally. High concentrations of pyrethroids or hyperactivity beyond what the cell can sustain will cause depolarization and conduction block. The pyrethroids that hold the sodium channel open the longest will cause the greatest amount of depolarization.

There is marked stereospecificity of the action of pyrethroids on the sodium channel; some isomers are more toxic than others (Soderlund, 1985, 2012; Meacham et al., 2008). The *cis* isomers are usually more toxic than the *trans* isomers. As an example, the 1*R* and 1*S cis* isomers bind competitively to one site, and the 1*R* and 1*S trans* isomers bind noncompetitively to another (Narahashi, 1986). In mammals the 1*R* isomers are active and the 1*S* isomers inactive, making the 1*S* isomers nontoxic. Deltamethrin has been produced using stereospecificity to

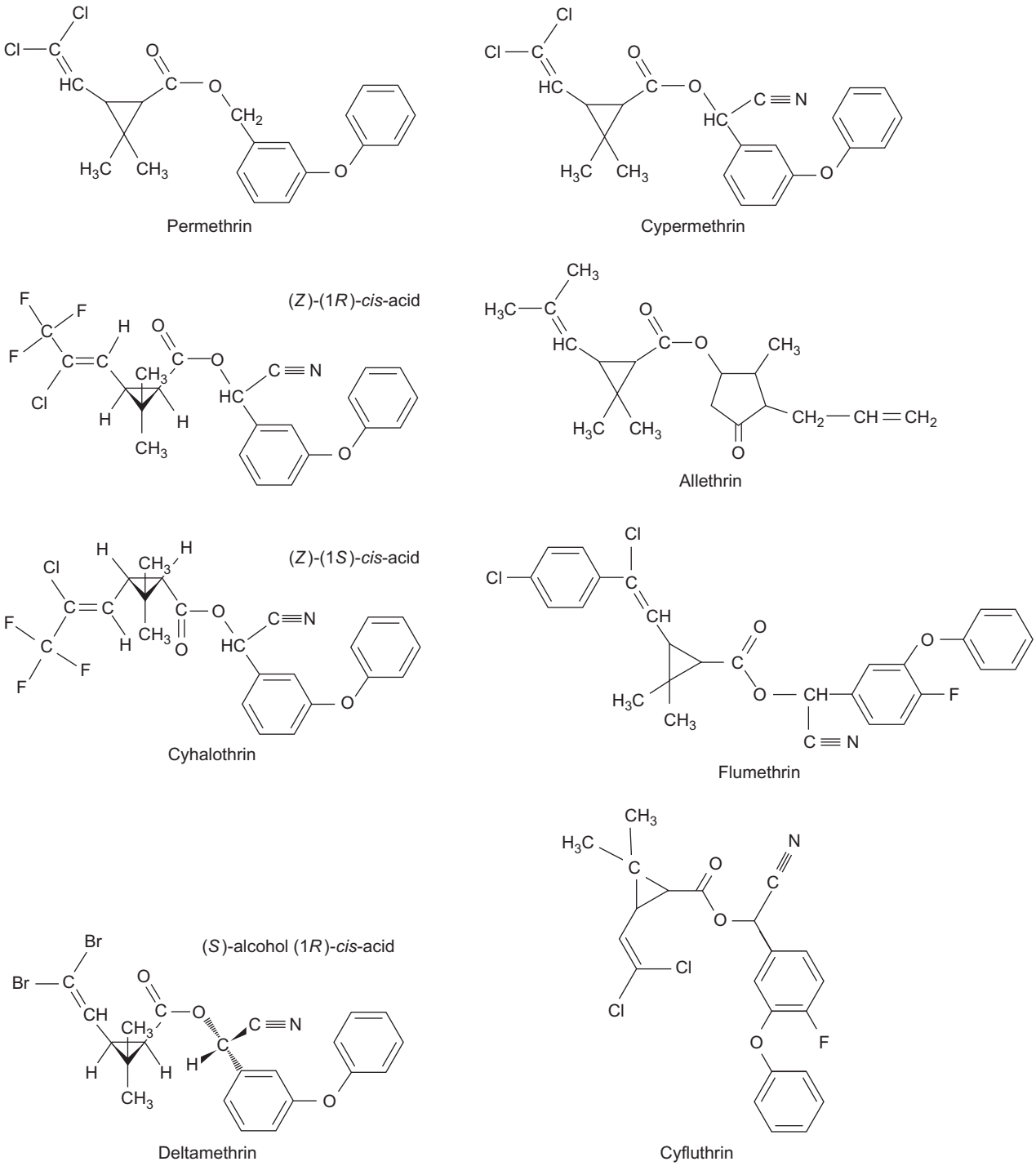

FIGURE 39.1 Structures of selected pyrethrins and pyrethroids.

produce a high degree of selective toxicity. This is the reason that the toxicity of different batches of pyrethroids can vary from batch to batch. The rat oral LD_{50} of commercial permethrin can vary from 430 to 8900 mg/kg, with toxicity depending on the amount of *cis* isomer present in the batch.

TOXICITY

Dermal exposure to pyrethroids is most common (Osweiler, 1996; Gammon et al., 2012; Anadon et al., 2013). In humans, the bioavailability of pyrethroids applied dermally is approximately 1%. Absorption after oral exposure in

humans is 36%, mostly from the stomach. Once absorbed, the pyrethroids are rapidly distributed due to their lipophilicity. Systemic distribution produces effects that can be difficult to control and may be confused with poisoning by other pesticides, such as organophosphates, which also cause increased salivation and hyperexcitability. Many pyrethroid formulations also contain solvents, which can also cause toxicity. Cats are very sensitive to pyrethroid exposure (Meyer, 1999; Malik et al., 2010).

The half-life of pyrethroids in general in plasma is in hours, while oral exposure can be equally short. Cyfluthrin has a plasma half-life of 19−86 min. Intravenous LD_{50}s for pyrethroids range from 0.5 to 250 mg/kg. The major neurotoxicity observed in adults with pyrethroid toxicity is acute toxicity with no chronic or cumulative toxicity being caused. The excitatory motor signs are generated at the spinal level.

Fish are highly sensitive to pyrethrin and pyrethroid products, and contamination of lakes, streams, ponds or any aquatic habitat should be avoided (Bradbury and Coats, 1986, 1989; Ansari and Kumar, 1988). Household exposure of fish can occur when the premise is sprayed or fogged with insecticides and the aquarium aerator is left on. The tank and aerator should be covered during use of insecticides and the home should be well ventilated before uncovering and starting the pump.

Most avian species are thought to be tolerant of pyrethrin and pyrethroid products but carriers or propellants in spray formulations may be hazardous (Bradbury and Coats, 1982). There is very little literature about pyrethrin or pyrethroid toxicity of exotic avian species, reptiles or lagomorphs.

Tables 39.1 and 39.2 reference the oral toxicity of some type I and II pyrethroids.

In dogs, cats and large animals the clinical signs are similar for both type I and II compounds. Clinical signs include salivation, vomiting, hyperexcitability, tremors, seizures, dyspnea, weakness, prostration and death (Murphy, 1996). In rats with type I toxicity there is an increased response to stimulation, muscle tremors, excitement and paralysis (Beasley et al., 1994). These clinical signs can also be compatible with strychnine toxicities. Type II overexposure will cause increased salivation, weakness, and choreoathetosis. The concomitant use of pyrethrins and pyrethroids with synergists such as piperonyl butoxide, organophosphorus compounds or carbamates may increase toxicity by mechanisms involving inhibition of microsomal oxidation (Anadon et al., 2009, 2013).

TABLE 39.1 Toxicity of Selected type I Pyrethroids

Type I Compounds	Oral LD_{50} (mg/kg body wt.) in Rat
Pyrethrin I	900
Allethrin	680
Tetramethrin	4640
Resmethrin	100
Permethrin	2000

TABLE 39.2 Toxicity of Selected type II Pyrethroids

Type II Compounds	Oral LD_{50} (mg/kg body wt.) in Rat
Cypermethrin	500
Deltamethrin	31
Fenvalerate	450
Fluvalinate	1000

These insecticides, in addition to neurotoxicity, can also produce hepatic, renal, dermal, cardiac, neurobehavioral, endocrine disruption, reproductive, and developmental effects in animals and humans (Vijverberg and van den Bercken, 1990; Wolansky and Harrill, 2007; Gupta, 2009; Drago et al., 2014; Atmaca and Aksoy, 2015; Hossain et al., 2015; Botnariu et al., 2016; Slima et al., 2016; Malik et al., 2017).

TREATMENT

There is no specific antidote for pyrethroid toxicity; animals should be treated symptomatically. The main treatment for dermal exposure is to wash the animal with a mild detergent and water. Do not use any shampoos that contain additional insecticides as this could increase exposure to insecticides. Large and small animals should be treated the same. The pyrethroids bound to the skin cannot be removed by washing with soap and water, but dermal paresthesia can be reduced by applying corn oil to the site(s) of application. For oral exposure, emetics or gastric lavage can be used to empty the stomach, if done within 1−2 h of ingestion. Activated charcoal and a saline or sorbitol cathartic will reduce oral absorption and increase elimination.

Supportive therapy using diazepam or barbiturates to control hyperexcitability or seizures can be used. Phenothiazine tranquilizers should not be used because they can lower the threshold for seizures. Atropine can be used to control excess salivation or gastrointestinal hypermotility.

The prognosis for pyrethroid toxicity is usually good because of the low toxicity.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Pyrethroid insecticides, being of plant origin, are attractive to people that prefer to use organic insecticides on their companion animals or livestock, or who are engaged in organic food production. Pyrethrin insecticides, while toxic to selected species, have a wider margin of safety than organophosphate or organochlorine insecticides. Biomarkers of exposure to pyrethroids are being investigated (Gupta and Milatovic, 2014). Urine is the matrix that is being most heavily investigated to determine which metabolites can be used to identify exposure to the parent compound. Advances in analytical methods to detect low concentrations of the pyrethroid metabolites will allow improved assessment of exposure in the future.

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