Review Article

Pyrethroid Insecticide Toxicity: Current Concepts and Review of Literature

Tanuj Kanchan,* Pradhum Ram**

ABSTRACT

Pyrethroids are synthetic organic compounds synthesized from chrysanthemum flowers that are used extensively as household and commercial insecticides. The keto-alocoholic esters of chrysathemic and pyrethroic acid being lipophilic are responsible for its insecticidal properties. Pyrethroids are broadly classified into first and second generation pyrethroids. The first generation (Type I) pyrethroids are less toxic to mammals than the second generation (Type II) pyrethroids.

Pyrethroids act by a variety of mechanisms which are primarily directed towards the sodium and chloride channels. The main route of absorption is through the skin as a result of occupational exposure. Inhalational exposure and ingestion remain the other routes of poisoning.

Local skin exposure produces paraesthesiae due to hyperactivity of cutaneous sensory nerves that is usually self-resolving. Following inhalational exposure, nasal and respiratory irritation can occur. Asthma-like symptoms have been observed. Massive doses have resulted in symptoms of pulmonary oedema. Mild eye irritation and miosis can occur on ocular exposure.

In the event of a poisoning, timely intervention is required. No specific antidote is available for pyrethroid poisoning and the management remains supportive and symptomatic.

The incidence of poisoning and death from pyrethroid poisoning is reportedly low due to the fact that extremely large doses are required for lethal effects, and a large number of cases go unreported, either due to mis-diagnosis or due to lack of an efficient system for recording and reporting of such events.

Key Words: Insecticide; Pyrethroid poisoning

Introduction

Acute poisoning is a leading cause of morbidity and mortality worldwide and thus, a serious global health concern. In India, poisoning is one of the preferred means of committing suicide,[1,2] and pesticides such as organophosphorus compounds and phosphides are frequently implicated in fatal poisonings.[3-5] Besides, unintentional poisoning from household poisons is also not uncommon.

Pyrethroids are commonly used synthetic organic compounds developed for their insecticidal properties. They are found in a large number of products used indoors as domestic pesticides, and for agricultural purposes on crops, and in gardens. Pyrethroids have been the insecticides of choice for consumers in the last few decades, and are important constituent of aerial sprays to kill or repel flying insects, ants, cockroaches, etc., as well as mosquito repellent coils, mats, and pastes. Some compounds are used topically in the treatment of scabies and head lice.

*(*Author for correspondence*): Dept of Forensic Medicine, Kasturba Medical College (Affiliated to Manipal University), Mangalore, Karnataka. E-mail: tanujkanchan@yahoo.co.in; tanujkanchan@manipal.edu

**Undergraduate Medical Student, Kasturba Medical College (Affiliated to Manipal University), Mangalore, Karnataka.

Structurally, pyrethroids are the synthetic analogs of naturally occurring pyrethrins present in the dried chrysanthemum (*Chrysanthemum cinerariifolium*) flower extract. Toxicity of pyrethroids insecticides is approximately 2250 times more to insects than mammals, and relatively few cases of pyrethroid poisoning have been reported in literature.[6] In a study from the USA, traces of at least one pyrethroid metabolite were found in 75 percent of the people tested during 2001–2002.[7] Severe poisoning from pyrethroids is uncommon in developed countries, but relatively common in developing countries due to its wide use in agriculture.[8] Despite their popular use in Indian households, with the possibility of intentional or unintentional exposure and related morbidity and mortality, reliable statistics on its effects are lacking.

Chemical Structure, Types and Classification

Natural pyrethrins are known to have insecticidal properties. However, they are unstable when exposed to sunlight. Hence, structure of pyrethrins was modified to produce more stable derivatives with insecticidal properties.[9] Pyrethroids are synthesized from the oleo-resin extract of dried chrysanthemum flowers. The organic extract is converted into acid form. The keto-alocoholic esters of chrysathemic and pyrethroic acid are lipophilic and responsible for their insecticidal properties. Allethrin was the first commercial pyrethroid that was identified way back in 1949.[6,10]

Pyrethroids are broadly classified as first generation (Type I) and second generation (Type II) compounds. Type I pyrethroids have a basic cyclopropane carboxylic ester structure. These are unstable in natural light and thus, of not much use in agricultural settings. Type II pyrethroids on the other hand, are more stable and resistant to air and sunlight and thus, suitable for use in the field of agriculture. Insecticidal property of Type II pyrethroids is enhanced due to addition of a cyano group. Type I pyrethroids are less toxic to mammals, whereas Type II compounds possess irritant and/or sensitizing properties and thus, more toxic to mammals.[6] Some of the Type I pyrethroids are allethrin, resmethrin, phenothrin, bioallethrin, and permethrin, while Type II pyrethroids include deltamethrin, cyphenothrin, cypermethrin, fenvalerate, and fluvalinate. Pyrethroids are broad spectrum insecticides, and more effective componds are continuously being developed that are less toxic to humans. Research has shown that presently, highly effective methyl-ester pyrethroids are easily synthesizable.[11] A few of the commonly used pyrethroids and their commercial preparations are listed in **Table 1**.

Mechanism of Action

Pyrethroids act by a variety of mechanisms. However, the primary mechanism of action is related to their high affinity for membrane sodium and chloride channels. Thus, nerve and muscle cells are the primary targets of pyrethroid action. Pyrethroids act on the voltage sensitive sodium channels (VSSCs) and cause sodium ion channels to open at more hyperpolarized potentials, thereby keeping them open for longer duration allowing more sodium ions to cross, resulting in protracted sodium influx (sodium tail current). The duration of the tail current is determined by the structure of the pyrethroid and is independent of its concentration. Type I compounds have been found to keep the channels open for shorter periods of time than Type II compounds. The latter are also known to act on the voltage dependent chloride channels. They decrease chloride channel conductance. At higher concentrations they are known to act on GABA-

Table 1 Pyrethroid Insecticides and Some Commercial Brands

Pyrethroid	Classification	Commercial Brand
Allethrin	First generation (Type I)	Baygon mats
D-Allethrin (Isomer of Allethrin)	First generation (Type I)	Baygon knock-out aerosols and Power mats, HIT insect repellent, Good Knight mosquito mats
Permethrin	First generation (Type I)	Permethrin, Ambush, Lee
Deltamethrin	Second generation (Type II)	Hexit
Decamethrin	Second generation (Type II)	Decathrin
Cyhalothrin	Second generation (Type II)	Karate, Reeva

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gated chloride channels which may be responsible for the seizures seen in severe type II pyrethroid poisoning.[6] Besides, voltage sensitive calcium channels (VSCCs) may also be important targets of pyrethroid action.[12] Peripheral benzodiazepine receptors are also proposed as target of pyrethroids.[6]

Increased toxicity of pyrethroids to insects when compared to mammals is principally due to poor absorption of pyrethroids and a rapid rate of metabolism in mammals. The insects in contrast have increased sodium channel sensitivity, smaller body size and lower body temperature which make them more vulnerable to the effects of pyrethroids. Pyrethroid toxicity does not cause any structural damage, but manifests instead as disordered function.[6]

Acute and Chronic Exposure and Toxicity in Humans

Exposure to pyrethroids occurs mainly through dermal contact, inhalation following unintentional use in households, and following occupational exposure. Intentional or unintentional ingestion of pyrethroids is the other route of exposure. Deliberate intravenous injection of a pyrethroid insecticide was reported recently by Gheshlaghi et al.[13] Systemic toxicity of pyrethroids is low as they are poorly absorbed through skin, and only moderately from the respiratory and gastrointestinal tracts. Metabolism is rapid and the metabolites are excreted in urine.

Pyrethroids have irritant and/or sensitizing properties. Acute dermal exposure is characterized by stinging, burning, and tingling sensation, numbness, erythema and allergic dermatitis, intense pruritus and blistering. Paraesthesiae represent the main adverse effect, which are self-resolving (usually within 24 hours). Ocular exposure may lead to irritation of eyes, itching, lacrimation, and conjunctival and lid oedema. Rarely, corneal damage may occur. Inhalation exposure of pyrethroids leads to asthma-like symptoms, and can also cause irritation of nasal and respiratory mucosa with sneezing, stuffiness of nose, and scratchy throat. Wheezing, dyspnoea, cough, chest pain, pneumonitis and pulmonary oedema may follow. Ingestion of pyrethroids causes irritation of the gastro-intestinal tract with nausea, vomiting, diarrhoea, anorexia, abdominal cramps, and tenesmus.

Systemic toxicity is characterized by fatigue, dizziness, headache, fasciculations, incoordination, tremors, and seizures. Large doses (200–500 ml) of concentrated formulations may cause hypotension, tachycardia, seizures and coma. Coma and convulsions are potentially life-threatening features of pyrethroid poisoning. Death in pyrethroid exposure usually occurs from respiratory failure.[6,14,15] In an epidemiological study on occupational acute pyrethroid poisoning in cotton farmers, adverse effects of pyrethroid exposure were observed in more than 1/4th of the participants.[16] Very few participants in the study showed significant systemic symptoms. In a study from Korea,[17] of all the cases of pyrethroid poisoning, 80% cases had ingested pyrethroid preparations intentionally. Fatal outcome was reported in 10% cases and cause of death was reported as respiratory failure.

Symptoms observed in poisoning with Type I pyrethroids and Type II pyrethroids vary, and two basic poisoning syndromes are observed. It is reported that Type I pyrethroids cause a Type I poisoning syndrome characterized by reflex hyperexcitability and fine tremor, whereas Type II pyrethroids induce salivation, hyperexcitability, choreoathetosis, and seizures.[18] Chronic exposure usually does not result in any specific long-term effects. It is believed that pyrethroids are unlikely to cause chronic toxicity in humans.[6,16]

A few uncommon presentations after acute exposure of pyrethroid preparations have been reported in literature. Ghosh et al[19] have reported a rare case of deltamethrin poisoning presenting with status epilepticus following deliberate ingestion of anti-lice medication. Status epilepticus has also been reported following intravenous injection of pyrethroid insecticide cypermethrin in a case of attempted suicide.[13] A case reported by Bhasker et al[20] raises a possibility of development of cardiac arrhythmias in pyrethroid poisoning due to their effect on sodium channels in the heart.

Management

Management of pyrethroid poisoning consists of pre-hospital care, diagnosis and hospital care. The basic outline of the management of pyrethroid poisoning is shown in **Fig 1**. Pre-hospital treatment of pyrethroid poisoning primarily consists of detoxification. The patient should be moved to fresh air immediately, and exposed skin should be washed promptly with copious amounts of soap and water. In cases of ocular exposure, the eyes should be washed immediately and continuously with water or saline. The patient should be shifted to the nearest hospital at the earliest. There is no specific antidote for pyrethroid poisoning, and the treatment is symptomatic and supportive. Airway, breathing and circulation should

be maintained, and specific symptoms treated with recommended drugs and doses (**Table 2**).

Vitamin E oil preparations may be used for the treatment of paraesthesia. Paraesthesia are usually self-resolving; however local application of vitamin E preparations have been found to lower the severity of skin reaction.[6] Gastric lavage should be conducted in cases reported early to the hospital when large amounts of pyrethroids are ingested. In cases of seizures, gastric lavage should be conducted once the seizures have been controlled. Isolated brief convulsions do not require treatment. However, prolonged seizures should be treated with intravenous benzodiazepines.[6] Atropine and oximes are not indicated in pyrethroid poisoning. Mild to moderate intoxication is usually characterized by spontaneous recovery. Prognosis is usually good with full recovery even in severely poisoned patients.

The diagnosis of pyrethroid poisoning is primarily based on the history of exposure. Exact diagnosis is difficult since the symptoms may be non-specific. Commercial preparations of pyrethroids are often combined with other substances such as organic solvents making the diagnosis further difficult. A serious problem with the diagnosis of pyrethroid poisoning is its close resemblance to organophosphate poisoning.[6] However, serum cholinesterase levels are observed to be normal in pyrethroid poisoning. Pyrethroids can be analysed easily by chromatography,

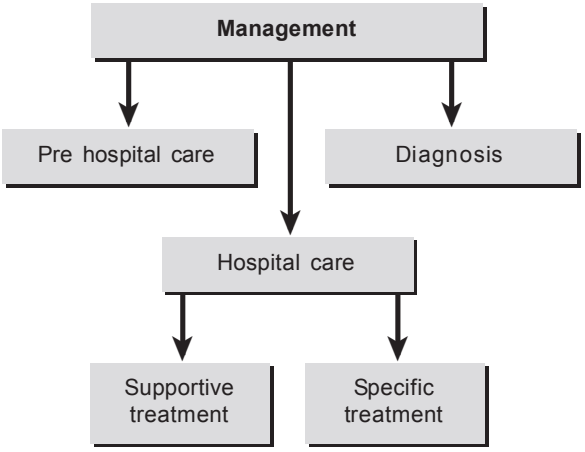

Fig 1 Basic Outline of Management of Pyrethroid Poisoning

the most appropriate detection systems being gas chromatography-flame ionization detector (GC-FID) and gas chromatography-mass spectrometer (GC-MS).

Conclusion

Pesticide/insecticide exposures usually are seen to be agriculture-related, or to rural settings. However, urban and semi-urban homes are equally prone to pyrethroid exposure, these compounds being in fact the most common pesticides at home. Though exact human health risks are unknown, pyrethroids are a potential environmental

Table 2 Recommended Drugs & Doses for Supportive Therapy

Symptoms	Drug	Dose
Hypotension	Dopamine	4–6 mcg/kg/min
Convulsions	Diazepam	Adult: 5–10 mg IV slowly Max dose: 30 mg Child: 0.25–0.40 mg/kg IV slowly Max. dose: 5 mg (upto 5 years) Max. dose: 30 mg (5–10 years)
Allergic reactions	Diphenhydramine	Adult: 50 mg oral/IV/IM, then 25–50 mg every 4–6 hrs for 24–72 hrs. Child: 2 mg/kg oral/IV/IM, then 5 mg/kg/days in 4 divided doses for 24–72 hrs.
Asthma	Aminophylline	Adult: 250 mg/10 ml IV very slowly Child: 7.5 mg/kg IV very slowly
Anaphylactoid reaction	Adrenaline	Adults: 0.3–0.5 mg (1:1000) SC 0.25 mg IV well diluted and given slowly Child: 0.01 mg/kg(1:1000) SC

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hazard. They have been shown to be toxic to aquatic organisms. Animal studies have linked pyrethroid exposure to damage of thyroid, liver and nervous system and impaired behavioural development, changes in immune system, and disruption of reproductive hormones. Fatal and non-fatal cases of human exposure are also reported, though rarely. The low incidence of poisoning and death from pyrethroid poisoning can be attributed to the fact that extremely large doses are required for lethal effects, and a large number of cases go unreported, either due to mis-diagnosis or due to lack of an efficient system for recording and reporting of such events.

The golden rule in prevention of poisoning is safe use and secure access. Pyrethroid insecticides should be used judiciously and cautiously in households so as to avoid accidental exposure at home, and preventive measures should be followed to prevent occupational exposure at work, e.g., using only recommended doses, and by wearing protective clothing, goggles, caps and gloves. Pyrethroids should be kept away from the reach of children to prevent accidental exposure.

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