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Review Article

An Assessment of Toxicological Profile of Pyrethroids in Animals - A Review

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Abstract

The review aims to highlight the toxic effects of pyrethroids-one of the commonly used insecticides worldwide. Earlier after their introduction in the market, they were considered safe and ineffective against non target species. However, now studies have confirmed that safety label against them turns out to be wrong. They are reported to cause acute, sub acute, chronic toxicities. Untoward changes have been reported in hematological, biochemical, oxidative stress and various reproductive parameters of exposed animals. These problems can been more in India and other developing countries because of indiscriminate use in agriculture, veterinary, medical and household pest control.

Keywords

Chrysanthemum cinerariaefolium

Pyrethroids

Toxicity

Introduction

The concept of pesticide use has been old age. Since before 2500 BC, humans have utilized pesticides to protect their crops. The first known pesticide was elemental sulfur dusting used in Sumer about 4,500 years ago. By the 15th century, toxic chemicals such as arsenic, mercury and lead were being applied to crops to kill pests. In the 17th century, nicotine sulfate was extracted from tobacco leaves for use as an insecticide. The 19th century saw the introduction of two more natural pesticides, pyrethrum which is derived from chrysanthemums, and rotenone which is derived from the roots of tropical vegetables (Miller, 2002). After World War II, the use of pesticides mushroomed and there are current more than 1,600 pesticides available

and about 4.4 million tons used annually at a cost of more than $ 20 billion (Ware, 1994). These insecticides primarily belonged to four major groups *viz.*, organochlorines, organophosphates and carbamates. Recently pyrethroids have gained importance in agriculture and veterinary health practices.

Pyrethroids were developed as pesticides from extracts of dried and powdered flower heads of *Chrysanthemum cinerariaefolium.* The active principles of these are esters of chrysanthemumic acid or pyrethric acid and cyclopentanone alcohols (cinerolone, jasomolone and pyrethrolone). The naturally occurring pyrethins have disadvantage that are rapidly decomposed by light. In order to overcome this problem, synthetic pyrethroids were developed and tested. The first commercial synthetic pyrethroid allethrin was developed in 1949 and the period 1960s saw different pyrethroids coming to the market which included dimethrin, tetramethrin and resmethrin. These pyrethroids were without cyano group and were usually referred as type-I pyrethroids However, addition of cyano group to these pyrethroids enhanced insecticidal activity and form type-II pyrethroids**.**

The general view that pyrethroids are safe to humans and other non-target mammals is supported by the fact that inspite of their long history of use, relatively few reports of pyrethroid toxicity have been reported (He et al., 1989; Peter et al., 1996). This low acute toxic effect is due to their quick metabolism and excretion in the form of non-active metabolites in urine of exposed animals (Lukowick-Ratajczak and Krechniak, 1991). This feature of pyrethroids in addition to their excellent knock down insecticidal properties (Elliot et al., 2005) and rapid degradation in soil (Agnihotthrodu, 1988) has led to their widespread use for more than 3 decades (Shafer et al., 2005). Therefore, not surprisingly these chemicals account for 30 per cent of insecticides used globally (Prasanti et al., 2005). Though severe toxicity of pyrethroids has been uncommon in developed countries, it appears common in developing countries because of their extensive and intensive use for agriculture and domestic purposes (Kakko et al., 2003). Available literature suggests that pyrethroid exposure is of considerable magnitude in India and other countries including the United States (Bateman, 2000; Narahashi, 2000). Humans and animals being the part of ecosystem are constantly exposed to these chemicals from environmental contamination or due to their high concentration in different food products or from inadvertent therapeutic applications or accidental and occupational exposure (Daniel and Moser, 1993).

Toxicokinetics

Pyrethroids are absorbed through oral and dermal routes with dermal absorption likely to be less as compared to oral (Nassif et al., 1980; Chester et al., 1987; Eadsforth et al., 1988; Van der Rhee et al., 1989; Woollen et al., 1992). However, this route is most significant for agricultural applicators and sprayers (Zhang et al., 1991). It has also been reported that absorption of pyrethroids through the gastrointestinal tract and the skin is variable and depends upon the vehicle of administration (Clark, 1995; Bateman, 2000; Soderlund et al., 2002). Comparative toxicity studies have also demonstrated that absorption of pyrethroids from respiratory tract is also effective (Adamis et al., 1985; Chen et al., 1991).

After absorption pyrethroids are rapidly distributed throughout body, mainly in the adipose tissue, stomach, intestines, liver and kidney and in the nervous tissue. They are rapidly and extensively metabolized mainly in the liver to their inactive acid and alcohol components probably by microsomal carboxyl esterase (Hutson, 1979; Ray, 1991). Further degradation and hydroxylation of alcohol occurs at position 4' and produces a wide range of metabolites (Hutson, 1979; Leahey, 1985). There is some stereospecificity in metabolism with trans-isomers being hydrolyzed more rapidly than cis-isomers (Soderlund and Casida, 1997). The pattern of metabolites has been reported to vary between oral and dermal exposures (Wilkes et al., 1993). Following dermal dosing with cypermethrin the ratio of trans/cis cyclopropane acids excreted was approximately 1:1 as compared 2:1 following oral administration in humans (Woollen et al., 1992). Organophosphates are thought to compete with pyrethroids for this hydrolysis and for this reason simultaneous exposure of organophosphates may cause pyrethroids toxicity (Ray and Forshaw, 2000).

Pyrethroids do not accumulate in the body and their excretion is rapid even after repeated administrations. Typically, 90% of the administrated dose is excreted in urine and faeces within a week after treatment (Aldridge, 1990; Vijverberg and Van der Brecken, 1990). Studies carried on human volunteers have shown that after oral administration of 0.25, 0.5 and 1.5mg/subject about 70% of the dose was excreted in 24

hours and the rate of excretion was similar for all doses (Van Sittert et al., 1985). Bifenthrin is excreted mainly as metabolites in urine but an unchanged proportion is also excreted in faeces. Rats treated with 4 to 5 mg/kg bifenthrin excreted 70% of insecticide in urine and 20% in faeces within 7 days and the remaining bifenthrin was found to get accumulate in tissues with high fat content such as skin and testes in males and the ovaries in case of females (US EPA, 1987).

Mechanism of action

Pyrethroids modify the gating characteristics of voltage-sensitive Sodium channels in mammals and invertebrate neuronal membranes to delay their closure (Narahashi, 1989; Ellis et al., 1992). The prolonged opening of Sodium channels by the neurotoxic isomers of pyrethroids produces a protracted Sodium influx which is referred to as Sodium "tail current". This lowers the threshold of sensory nerve fibres for the activation of further action potentials leading to repetitive firing of sensory nerve endings (Vijverberg and Van den Bercken, 1990) which may progress to hyperexicitation of the entire nervous system (Narahashi et al., 1995). Pyrethroids after impairing of ion transport through the membrane of nerve axons are responsible for muscular paralysis in the insects. Death seems to follow a nervous system impairment that occurs a few minutes after pesticide absorption (Reigart and Roberts, 1999).

Pyrethroids without an alpha cyano group like bifenthrin cause a moderate protraction of the sodium channel permeability in the nerve while alpha cyano pyrethroids like deltamethrin cause a long lasting protraction of the nerve membrane during excitation (US EPA, 2000). Invertebrates and some cold-blooded species are more susceptible to the toxic effects of pyrethroids than vertebrates (Narahashi et al., 1995). The interaction of pyrethroids with macromoleculer components of the sodium channel is reversible. Removal of pyrethroids from the nervous system is rapid with 50 per cent recovery of effects have been shown to occur from 30 min. to 3-4 hrs after poisoning (Aldridge, 1990). Interaction with Sodium channels is not the only mechanism of action proposed for pyrethroids in insects and vertebrates (Ray and Forshaw, 2000).

Some authors have suggested that effects on the central nervous system depend on an antagonism of gamma-amino butyric acid (GABA)-mediated inhibition, modulation of nicotinic cholinergic transmission, enhancement of nor-adrenaline release and action on calcium channel (Ray and Forshaw, 2000; Soderlund et al., 2002).

Pyrethroid toxicity

Acute toxicity

Two distinct acute syndromes reported to be induced by pyrethroids in mammals are described as T and CS syndrome. The so called "T-syndrome" is characterized by tremors, extreme sensitivity to sensory stimuli, ataxia, convulsions and paralysis. The so-called "CS syndrome" is characterized by hypersensitivity to external stimuli, choreoathetosis (sinuous writhing), salivation and in some cases paralysis (Narahashi, 2000).

Systemic toxicity after dermal exposure to pyrethroids is low (Clark, 1995). However, pyrethroids have been reported to produce effects on skin which include scratching, licking or biting at the site of dermal application and the symptoms usually occurred within 1 hour after application (Cagen *et al.*, 1984). Bifenthrin has been reported to cause irritation and tingling sensation of human skin which lasts for several hours (US DHHS, 1993)

Exposure of pyrethroids through respiratory route is accompanied by hypothermia without clinical signs (Pauluhn et al., 1996; Pauluhn and Machemer, 1998). Pyrethroid-related sensory irritation in the respiratory tract was carried out in rats and mice and it was reported that rats are more susceptible than mice to (Pauluhn et al., 1996).

Sub-acute toxicity

The main target organ for short-term toxicity of pyrethroids is the nervous system. Daily oral administration of cyhalothrin in mice at levels of up to 2000 mg/kg diet for 28 days showed toxic effects at dosages of 100 mg/kg and above. The observed effects were dose-related and included ataxia and hypersensitivity to external stimuli (IPCS, 2000). Lakkawar et al. (2004) studied the effect of cypermethrin in rabbits and observed that dullness, anorexia, reduced feed intake, diarrhoea, hyper-irritability, salivation, weakness and paralysis was the characteristic signs of the toxicity. Bifenthrin when taken in large doses has been reported to cause

incoordination, tremor, salivation, vomiting, diarrhoea and irritability to sound and touch (USDHHS, 1993).

Hartym-Maj (2000) reported that 28 day treatment of mice with deltamethrin caused significant decrease in body weight. Decrease in body weight due to deltamethrin in mice was also reported by Madsen et al. (1996). Luty et al. (2000) conducted the intoxication experiment of cypermethrin in mice and observed that during first week of experiment there was a significant decrease in body weight which was followed by increase in body weight in third week. Lakkawar et al. (2004) reported significantly decreased body weight in cypermethrin treated rabbits as compared to control groups.

Hematological alterations

Short term exposure studies of pyrethroids have been carried out in rats and other animals for finding out their effect in haematology and biochemistry. Mohamed (1988) treated rats with fenvalerate and observed significant reduction of TEC, PCV and Hb. Similar findings were reported by Parker et al. (1984) and Singh et al. (2001) in fenvalerate treated dogs and cockerels respectively. Quadri et al. (1987) observed decrease in Hb, PCV and TEC in cypermethrin treated chickens. Tosluty et al. (2001) studied the effect of deltamethrin and fenvalerate on blood parameters in mice and observed that irrespective of the dose these pyrethroids caused increase of Hb and PCV where as in female mice, the administration of deltamethrin resulted in suppression of Hb and PCV values. It was also reported that irrespective of dose of deltamethrin and fenvalerate and sex of animal there was increase in the number of leucocytes. Manna et al. (2005) studied the effect of deltamethrin in rats after oral administration and observed decreased PCV, Hb and TLC in treated animals as compared to control group.

Biochemical alterations

Patel et al. (2001) demonstrated that single oral dose of cypermethrin in cross bred calves caused significant increase in transaminase activity. Kaur et al. (2001) observed that repeated oral administration of deltamethrin and cypermethrin in buffalo calves caused increase in the levels of AST, ALT, ACP and ALP. Shah and Gupta (2001) reported increased activities of AST, ALT without significant changes in BUN, creatinine and total plasma protein in permethrin treated rats. Manna et al. (2005) studied that repeated oral dose of deltamethrin in rats caused increased activity of serum amino transferases and alkaline phosphatase in treated animals as compared to control group.

Tendon (1990) and Garg et al. (1997) reported fenvalerate and fluvalinate respectively caused significant inhibition of cholinesterase in rats. Przebirowska et al. (2001) reported dermally applied chlorpyrifos and cypermethrin in mice caused significant inhibition of cholinesterase in serum and brain. Permethrin for a period of 7 days in rats did not produce any significant influence on plasma, erythrocyte, brain and liver ChE activities (Shah and Gupta, 2001). Yavasoglu et al. (2006) reported non-significant inhibition of liver cholinesterase in cypermethrin treated rats.

Reproductive and developmental toxicity

Pyrethroids do not impair the mating capacity and fertility in the experimental animals. The fertility of female rats was affected only for oral doses equal to 250 mg/kg/day or above and no evidence of teratogenic activity was observed in mice, rats or rabbits, even at doses that are able to produce clinical signs of maternal toxicity (Vettorazzi, 1979).

The reproductive toxic effects of bifenthrin observed in rats which was given about 1 mg/kg/day bifenthrin did not show toxic symptoms and the same results were obtained in rabbits which were fed 2.67 mg/kg/day bifenthrin (US EPA, 1987). The dose at which no toxic effects were observed on development was 1 mg/Kg/day for rats and greater than 8 mg/kg for rabbits (Walker and Keith, 1992). Regarding teratogenic effects bifenthrin did not demonstrate any teratogenic effects at highest levels (100 ppm, approximately 5.5 mg/kg/day) after testimg it in two generational studies in rats (US EPA, 1988).

Carcinogenicity

There was no evidence of cancer in a 2-year study of rats which were given 10 mg/Kg/day of bifenthrin. However 87 week feeding study of mice with doses of 7, 29, 71 and 86 mg/kg showed a significantly higher dose related trend of increased tumor incidence in the male urinary bladder and the incidence was significantly increased at 86 mg/kg/day (US EPA, 1988). The females had higher incidences of lung cancer due to bifenthrin

toxicity than the males (US EPA, 1987) The EPA has classified bifenthrin as a class C carcinogen, a possible human carcinogen.

Oxidative stress

Like other insecticides few reports have suggested that pyrethroids also produce oxidative stress in exposed animals. Kale et al. (1999) reported that cypermethrin and fenvelerate toxicity in rats caused increase in oxidative stress parameters like lipid peroxidation, SOD, GPx and catalase. Ahmet et al. (2005) studied cypermethrin induced oxidative stress in rats and found increase in MDA levels in brain and liver. Catalase activity in tissues except that of erythrocytes was found to decrease. GSH-Px activity in liver and erythrocytes was found to increase where as the activity of same enzyme was found to decrease in brain and plasma.

Manna et al. (2005) reported sub acute oral toxicity of deltamethrin caused increase in MDA levels and a decrease in levels of glutathione, SOD and catalase. Yousef et al. (2006) observed significant decrease in activity of GST and SOD in deltamethrin treated rats. Omotuyii et al. (2006) reported significant increase of TBARS, glutathione peroxidase and glutathione reductase in cyfluthrin treated rats Otitoju et al. (2007) demonstrated neurotoxicity of permethrin in rats and observed the insecticide caused increased levels of TBARS. Liver homogenates manifested significant increase in GST where as brain and plasma homogenates manifested decrease in the enzyme; the decrease was significant in brain and non-significant in plasma. Singh et al. (2009) observed decreased activity of GST in cyfluthrin treated rats. Raina et al. (2009) observed significant decrease in catalase, GPx, SOD and reduced glutathione in cypermethrin treated rats.

Conclusion

Pyrethroids though aimed at reducing the population of pests can produce subtle health problems in humans and animals in terms of changes in various haemato-biochemical profiles, oxidative stress indices and reproductive parameters. The problems can be more in developing countries where no regulation on their indiscriminate use is followed. Efforts, therefore, should be made to make awareness among users of these insecticides about untoward effects they can produce in the biological system of humans and animal and the surrounding environment.

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