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PHARMACODYNAMIC INTERACTIONS OF CYPERMETHRIN AND CENTRALLY ACTING DRUGS IN MICE

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Abstract: Cypermethrin a widely used insecticide of Pyrethroids (type II) group, was administered in mice at two dose levels (1/10 of LD50 i.e. 2.5 mg/kg and 1/5 of LD50 i.e. 5.0 mg/kg) and pharmacodynamic interactions of insecticide were studied with centrally acting drugs viz. pentobarbital sodium, amphetamine, pentylenetetrazole, acepromazine and analgin.

Cypermethrin pretreatment potentiated the actions of pentobarbital and pentylene-tetrazole as evidenced by an increase in pentobarbital induced hypnosis and duration of pentylene-tetrazole induced chemoshock seizures.

Tranquilizing action of acepromazine was potentiated but there was decrease in amphetamine influenced locomotor activity at both the dose levels. Cypermethrin pretreatment, however, did not have any pharmacodynamic interaction with analgin.

Key words: centrally acting drugs, cypermethrin, mice, pharmacodynamic interactions

INTRODUCTION

Synthetic pyrethroids have emerged as potentially useful group of insecticides with high insect/mammal toxicity ratio, rapid detoxication in mammals and lack of cumulative toxicity (1).

Though, these compunds are relatively safe on the basis of conventional toxicity tests, some of the recent studies (2, 3, 4, 5) have shown neurotoxic potential of synthetic pyrethroids. In view of these observations, the present studies were undertaken to study possible pharmacodynamic interactions of the insecticide with centrally acting drugs such as pentobarbital sodium, pentylene-tetrazole, acepromazine, amphetamine and analgin.

METHODS

Male Swiss albino mice (20-28 g), obtained from disease free Small Animal House, Hissar were used. The animals were maintained on standard diet and feed & water were provided *ad libitum*. Cypermethrin (Ripcord, 10 EC, Nocil, India) was dissolved in sterile normal saline and was administered intraperitoneally at two dose levels i.e. 2.5 mg/kg (1/10 of LD_{50}) and 5.0 mg/kg (1/5 of LD_{50}). Centrally acting drugs (Pentobarbital sodium, acepromazine, amphetamine, analgin and pentylene-tetrazole) for which interactions were to be studied were injected intrapertioneally 30 min post- cypermethrin administration. Control animals received isovolumetric amount of normal saline alone.

Following tests were conducted for studying pharmacodynamic interactions:

Pentobarbital interaction: Pentobarbital sodium was injected at 50 mg/kg, ip. The time during which there was loss of righting reflex was recorded as pentobarbital hypnosis time.

Acepromazine interaction: Interaction of acepromazine maleate, (2 mg/kg, ip) was studied in mice receiving cypermethrin at 2.5 and 5.0 mg/kg, ip and control animals with help of tread mill test using Techno Rotarod as per the method described by Kinnard and Carr (6).

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Amphetamine interaction: Pharmacodynamic interaction of amphetamine sulfate (5 mg/kg, ip) was studied on the basis of spontaneous locomotor activity of insecticide treated and control mice with help of 'Techno' Photoactometer.

Analgin interaction: Tail immersion test (7) was employed to study pharmacodynamic interactions of insecticide with analgin (200 mg/kg, ip).

Pentylene-tetrazole interaction: Duration (in min) of pentylene-tetrazole (70 mg/kg, ip) induced chemoshock seizures in insecticide treated and control mice was recorded to study the interaction.

Statistical analysis: Student 't' test was used to specify significant difference.

RESULTS

The mice administered insecticide at sublethal dose levels (1/5 and 1/10 of LD_{50})showed initial excitement followed by depression. The initial symptoms included hyperactivity and increased startle response. At later stages, animals showed incoordination and ataxia.

Cypermetrhin at the dose level of 5 mg/kg, i/p potentiated ($P < 0.05$) pentobarbital hypnosis (Table I). However, lower dose (2.5 mg/kg) failed to evoke such effect. Cypermethrin pretreatment (at both the dose levels) increased the duration of chemoshock seizures induced by pentylene-tetrazole. The severity of seizures was, however, reduced.

The inhibitory effect of acepromazine on muscle tone and balance as evident from rotarod studies, was potentiated with cypermethrin pretreatment. A significant incoordination in movements persisted upto 90 minutes post acepromazine administration. The effect was more pronounced at a higher dose level of cypermethrin.

The insecticide pretreatment significantly reduced ($P < 0.01$) amphetamine influenced spontaneous locomotor activity at 30 min at both the dose levels and this effect continued till 90 min.

Anagesic action of analgin (100 mg/kg) was not affected following simultaneous administration of cypermethrin (at doses of 2.5 and 5 mg/kg).

TABLE I: Effect of Cypermethrin on the duration of pentobarbital induced hypnosis and on pentylene-tetrazole induced chemoshock seizures.

Treatment (mg/kg)	*Sleeping time (min)*	*Treatment (mg/kg)*	*Duration of seizures (min)*
Pentobarbital sodium (50)	73.0±5.8	Pentylene-tetrazole (70)	35.0±5.23
Cypermethrin (2.5) + Pentobarbital sodium (50)	79.0±9.8	Cypermethrin (2.5) + Pentylene-tetrazole (70)	82.9±3.5**
Cypermethrin (5.0) + Pentobarbital sodium (50)	96.3±7.3*	Cypermethrin (5.0) + Pentylene-tetrazole (70)	91.0±2.7**

n=6;
*P<0.05;
**P<0.01

DISCUSSION

Cypermethrin produced an initial excitement followed by depression on gross examination of animals. Slight ataxia and motor incoordination were also observed within 15-30 min of administration.

Marked potentiation of pentobarbital hypnosis at the higher dose levels of cypermethrin could occur because of irreversible inhibition of mixed function oxidases (8).

Cypermethrin administration at lower dosage (2.5 mg/kg) however, failed to evoke any such response. Similar interaction with pentobarbital has been observed in mice with another synthetic pyrethroid, fluvalinate, in our earlier studies (9). An increase in the chemoshock seizure time could also be ascribed to the inhibition of mixed function oxidases.

Cypermethrin at both the dose levels significantly potentiated the motor incoordination (as evidenced by tread mill/rotarod test) induced by phenothiazine derivative, acepromazine. Yet another experiment (spontaneous locomotor activity by photoactometer) indicated that cypermethrin significantly reduced amphetamine influenced spontaneous locomoter activity. Neurotoxic symptoms such as motor incoordination, loss of muscle tone and reduced locomotor activity have been explained on the basis of increased levels of putrescine, spermidine and spermine concentration in

hypothalmus and hippocampus (3) or on increased levels of dopamine and norepinephrine contents and decreased level of 5-HT (5) in whole brain. Imbalance in neutrotransmitters of brain may, thus, lead to neurotoxic symptoms. In an another study (4), it has been shown that offspring of gestationally exposed rats show disturbances in development of extra pyramidal system characterized by decreased concentration of dopaminergic and muscarinic receptors and decreased activities of enzymes, Na^+K^+ATPase, monoamine oxidase and acetylcholinesterase. This may in turn lead to gait disorders and neuro-behavioural deficits.

The findings of the present investigation point a need for delineating site of neuro-toxic action of synthetic pyrethroids in view of their potential use in agriculture and animal husbandry practices. Furthermore, centrally acting drugs (anaesthetics, hypnotics, ataractics) should be given with great caution in animals being treated with synthetic pyrethroids for ectoparasiticidal action.

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