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REPEATED DOSE STUDY ON SYMPTOMOLOGY AND PATHOMORPHOLOGICAL CHANGES IN DELATAMETHRINE INDUCED TOXICITY IN WISTAR RAT

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The present investigation was under taken to study the sympytomology and pathomorphological effect of deltamethrin and mitigatory potential of Vitamin-E. It was assessed by studying the various parameters viz., symptomatology, weekly body weight, feed consumption and water intake and pathomorphological alterations in various visceral organs. Fifty adult Wistar rats were divided uniformly in to five groups as Group A, B, C, D and E. The Group A received 1 ml. Dimethylsulfoxide plus Vitamin-E 100 mg/kg b.wt. and served as control, Group B, C, D and E rats were daily treated with Deltamethrin (98 % pure) @ 7.5 mg/kg b.wt. (Group B and C) and 15 mg/kg b.wt. (Group D and E), along with Deltamethrin, Group C and E were daily supplemented with Vitamin-E 100 mg/kg b.wt. for 30 days. Rats of Group B and C showed a retrogressive feed intake, tendency to pawing of litter material and try to burrowing in it, mild sweating on back with stretching of limb and also exhibited signs of dullness and depression whereas, the intensity of toxic signs increased dose dependently in rats of Group D and E rats manifested toxic signs like copious salivation, whole body tremor, convulsion, severe sweating and paralysis of hind limb. In both male and female rats, there was dose dependant significant ($P<0.05$) reduction in mean value of average weekly feed consumption and No significant change in water intake was observed throughout the experiment in all treatment groups as compared to control. Dose dependant varying degrees of gross and histopathological lesions were observed in various organs viz., liver, kidney, lung, brain, heart, spleen, testis, stomach and intestine of the rats receiving two different dose of deltamethrin (7.5 and 15 mg/kg) with and without vitamin-E.

Key words: Clinical symptoms, Pathomorphological, Deltamethrin, wistar rat

Pyrethroid insecticides are one of the most widely used agrochemical that are constantly increasing in popularity. Out of all synthetic pyrethroids deltamethrin is more potent photostable an insecticide is being extensively used agriculture, animal husbandry practices, public health programme and pest control in environment, grain, food stuff etc. Because of indiscrimative use is this agrochemical, environmental pollution and residual effect on food stuff is likely to occur. The man and animal are exposed to low level of pesticides residues present in the air, water and food chain. The continuous use of pesticides even in normal recommended dose may produce deleterious effect on the physiological function of various body system (Chauhan *et al.*, 1994). With this toxicological point of view the present study of repeated dose deltamethrin toxicity was under taken in Wistar rats.

MATERIALS AND METHODS

Experimental design

Fifty colony bred Albino Wistar strain rats of both sexes, aged between six to eight weeks with body weight ranging from 200 g to 300 g were divided into six groups. Group A was kept as control while Group B to E was kept as treatment group. LD-50 value of deltamethrin in DMSO is 150 mg/kg was considered according to value determined by Manna, *et al.* (2005). Deltamethrin in two

different doses (dissolved in dimethylsulphoxude- DMSO) with and without Vitamin-E (dissolved in corn-oil) was given to all treatment group. Group B & Group C was received deltamethrin @ LD50/20 with or without Vit-E respectively and Group D & Group E was received deltamethrin @ LD50/10 with or without Vit-E respectively. All Rats of the treatment groups was received deltamethrin in 1 ml. DMSO.

All the experimental rats were closely observed for any behavioral change or mortality during the entire period of experiment. Feed consumption and daily water intake was also recorded. The body weight was recorded weekly.

Pathomorphological studies

Rats died during the course of experiment or sacrified after completion of 28 days were subjected to necropsy. All the visceral organs were thoroughly examined and the gross lesion, if any,were recorded carefully. Tissues pieces from affected lung liver, brain, heart, spleen, kidney, thymus, skin, stomach and testis were collected and subsequently preserved in 10 per cent neutral buffered formalin for at least 24-48 hours. Further these tissues were processed by routine method of dehydration in graded alcohol, clearing in xylene and embedding in paraffin. Sections of 5-6 µ thicknesses were prepared and processed by routine Hematoxylene and Eosin method to study the general histopathological alterations (Luna, 1968).

The statistical analysis of data generated on various parameters was subjected to statistical analysis using completely randomized design (CRD) (Snedecor and Cochran, 1980) and using CD values compared the treatment means.

RESULTS AND DISCUSSION

Clinical Symptoms

All the experimental rats were closely observed for development of clinical symptoms throughout the experimental period. Rats of Group B and C receiving deltamethrin at the dose level (7.5 mg/kg) with and without Vitamin-E showed a retrogressive feed intake, tendency to pawing of litter material and try to burrowing in it, mild sweating on back with stretching of limb and also exhibited signs of dullness and depression. Whereas the intensity of toxic signs increased dose dependently in rats of Group D and E those were receiving deltamethrin at high dose level (15 mg/kg) with and without Vitamin-E. Rats of this groups manifested toxic signs like copious salivation, whole body tremor, convulsion, severe sweating and paralysis of hind limb. The clinical signs observed in the present study were also observed by Glomot and Chevalier (1976), Hunter *et al.* (1977), Coombs and Clark (1978) and Rickard and Brodie (1985) in rats intoxicated with deltamethrin, Cantalamessa (1993) in rats treated with cypermethrin, Shivkumar *et al.* (2002) in rats, Suwanchaichinda *et al.* (2005) in mice, Manna *et al.* (2005) and David *et al.* (2006) in deltamethrin treated rats. Symptoms developed in rats after deltamethrin administration is depend on threshold level of deltamethrin in blood and brain and also the symptoms will persisted for as long as the threshold dose maintained (Rickard and Brodie, 1985). The effects of type-II pyrethroid on startle amplitude are mediated by an indirect metabolic effect and a direct effect at the site of muscle (Hijzen and Slangen, 1988).

The average weekly body weight (g) of males and females rats recorded in different groups have been summarized and presented in table1(male) and 2 (female). There was no significant reduction in body weight of male and female rats up to 7th day. The significant decreases in body weight was observed in all treatment groups from 14th day onward when compared with control group. The most significant dose dependent reduction at 28th day post treatment was observed in Group D followed by Group E, Group B and Group C rats when compared with control rats. The present finding of dose dependent significant decrease in body weight of male and female rats were coincided with the finding of Coombs *et al.* (1978) in rats, Goldenthal *et al.* (1980) in rats, Husain *et al.* (1996) and Haratym-Maj (2002) in mice intoxicated with deltamethrin. However, Myer (1989) in rats, Suwanchaichinda *et al.* (2005) in mice and Kilian *et al.* (2007) in rats treated with

Table: 1 Comparison of weekly body weight, feed consumption and water intake (Mean ± S.E., g) in male rats of different experimental groups (n = 5 rats).

- Superscripts are to be read column wise for mean comparison.

Parameters	Male					
	Days	Group A	Group B	Group C	Group D	Group E
Body weight (g)	0	281.00^{a} ± 3.391	281.20^{a} ± 2.702	281.00^{a} ± 2.646	280.60^{a} ± 2.361	281.00^{a} ± 2.264
	7	286.00^{a} ± 3.464	283.80^{a} ± 2.815	284.20^{a} ± 3.190	282.40^{a} ± 1.924	282.55^{a} ± 1.946
	14	291.20^{a} ± 2.764	279.20^{b} ± 2.200	279.60^{bc} ± 3.108	275.25^{d} ± 2.478	275.80^{de} ± 2.379
	21	294.20^{a} ± 2.010	272.40^{b} ± 2.522	273.60^{bc} ± 1.913	268.20^{d} ± 2.615	269.40^{de} ± 2.672
	28	299.40^{a} ± 2.182	270.40^{b} ± 2.205	270.60^{bc} ± 2.250	244.20^{d} ± 1.020	245.20^{de} ± 1.098
Feed consumption (g/day)	7	98.06^{a} ± 2.961	84.06^{b} ± 2.868	85.32^{bc} ± 4.000	72.81^{d} ± 2.399	73.78^{de} ± 2.603
	14	100.12^{a} ± 1.853	78.99^{b} ± 1.159	80.39^{bc} ± 2.509	68.63^{d} ± 0.877	70.55^{de} ± 1.125
	21	99.61^{a} ± 1.453	75.65^{b} ± 1.252	77.13^{bc} ± 2.352	66.80^{d} ± 1.753	67.90^{de} ± 1.285
	28	100.32^{a} ± 1.852	69.95^{b} ± 2.177	71.89^{bc} ± 1.635	61.77^{d} ± 1.994	62.38^{de} ± 2.088
Water intake (ml	7	147.85^{a} ± 2.375	144.00^{a} ± 2.035	145.28^{a} ± 1.686	145.14^{a} ± 1.993	144.42^{a} ± 1.645
	14	144.71^{a} ± 1.714	145.11^{a} ± 2.176	147.14^{a} ± 2.314	146.42^{a} ± 2.448	146.34^{a} ± 2.614
	21	145.57^{a} ± 1.888	146.84^{a} ± 2.798	145.57^{a} ± 2.339	145.17^{a} ± 2.187	148.42^{a} ± 2.458
	28	144.71^{a} ± 2.767	147.14^{a} ± 2.029	147.38^{a} ± 2.589	146.21^{a} ± 1.997	147.26^{a} ± 2.286

superscripts in column do not differ significantly ($P < 0.05$).

deltamethrin reported no effect on body weight. Seems that compound at relatively higher dose affect the feed consumption and body weight gain (Bhelonde and Ghose, 2004). Decrease in body weight gain in insecticide treated rats may be due to effect of insecticide on gastrointestinal tract resulting in decreased appetite and absorption whereas, other workers explained reduced body weight gain which might be an indication of direct general toxicity or stressogenic activity of these pyretroids compounds (Goyal *et al.*, 1986; Haratym-Maj, 2002).

The details of mean ± S.E. values of weekly feed consumption of male and female rats expressed in gram among different groups during experimental period are summarized and presented in table1(male) and 2 (female). In both male and female rats, there was dose dependant significant reduction in mean value of average weekly feed consumption throughout the experiment in all treatment groups as compared to control. The highest decrease in feed consumption was observed in male and female rats of Group D followed by Group E, Group B and Group C as compared to control rats. Reduction in feed consumption was also reported earlier by Rouaud and Marzin (1977^{a}) in mice, Rouaud and Marzin (1977^{b}) in rats treated with deltamethrin, Bloom *et al.* (1993) intoxicated rats with permethrin and cypermethrin treated rabbits by Lakkawar *et al.* (2004). However, Hunter *et al.* (1977) in rats, Goldentahl *et al.* (1980) in mice treated with deltamethrin and tetramethrin intoxicated rats by Hiromori *et al.* (1986) reported no effect on feed consumption. Reduction in feed consumption may be due to effect of

Table: 2 Comparison of weekly body weight, Feed consumption and Water intake (Mean ± S.E., g) in female rats of different experimental groups (n = 5 rats).

Parameters		Female				
	Days	Group A	Group B	Group C	Group D	Group E
Body weight (g)	0	208.80^{a} ± 1.000	209.20^{a} ± 1.851	208.80^{a} ± 2.702	209.00^{a} ± 2.500	209.20^{a} ± 2.043
	7	213.20^{a} ± 2.382	211.00^{a} ± 1.696	210.60^{a} ± 2.612	208.80^{a} ± 2.903	209.00^{a} ± 1.837
	14	217.60^{a} ± 2.015	207.80^{b} ± 1.882	208.00^{bc} ± 2.510	204.00^{d} ± 2.121	206.40^{de} ± 1.721
	21	220.60^{a} ± 1.860	201.00^{b} ± 2.236	202.20^{bc} ± 2.354	198.60^{d} ± 2.112	199.60^{de} ± 2.943
	28	226.80^{a} ± 1.357	193.40^{b} ± 1.965	194.20^{bc} ± 2.853	169.00^{d} ± 2.665	170.50^{de} ± 2.841
Feed consumption (g/day)	7	87.43^{a} ± 2.292	75.60^{b} ± 2.803	76.60^{bc} ± 2.495	67.07^{d} ± 1.739	68.35^{de} ± 1.693
	14	86.26^{a} ± 1.752	71.95^{b} ± 1.578	72.43^{bc} ± 1.669	64.15^{d} ± 1.511	65.30^{de} ± 1.959
	21	86.86^{a} ± 1.508	67.82^{b} ± 1.714	69.06^{bc} ± 1.451	62.41^{d} ± 1.110	64.28^{de} ± 1.203
	28	87.96^{a} ± 1.388	61.58^{b} ± 2.021	62.09^{bc} ± 1.985	56.25^{d} ± 2.259	57.84^{de} ± 1.615
Water intake (ml)	7	138.57^{a} ± 1.270	137.00^{a} ± 2.116	135.00^{a} ± 3.055	134.85^{a} ± 2.209	135.51^{a} ± 1.950
	14	136.27^{a} ± 2.616	135.48^{a} ± 1.822	135.42^{a} ± 2.580	136.14^{a} ± 2.940	137.46^{a} ± 2.067
	21	138.57^{a} ± 2.339	137.14^{a} ± 1.421	136.53^{a} ± 1.875	137.22^{a} ± 1.066	136.48^{a} ± 1.616
	28	136.14^{a} ± 2.087	137.00^{a} ± 2.401	135.57^{a} ± 1.343	138.42^{a} ± 2.477	138.85^{a} ± 2.434

- Superscripts are to be read column wise for mean comparison.
- Mean with similar superscripts in column do not differ significantly ($P < 0.05$).

insecticide on gastrointestinal tract resulting in decreased appetite.

The details of mean ± S.E. values of weekly water intake of male and female rats expressed in ml. among different groups during experimental period are summarized and presented in table1(male) and 2 (female). No significant change in water intake was observed in male and female rats of different experimental groups throughout the experimental period. The finding of the present study are agreemented with earlier reports of Hunter *et al.* (1977) and Hiromori *et al.* (1986) in rats intoxicated with deltamethrin and tetramethrin respectively. In contrast to this Lakkawar *et al.* (2004) reported reduction in water intake in rabbits treated with cypermethrin. Results of present study might be due to wide inter-individual variation, the differences due to treatment were rarely statistically significant.

Pathomorphological observation

Administration of various dose level of Deltamethrin (7.5 and 15 mg/kg) with and without Vitamin-E (100 mg/kg) for 30 days were observed for various macroscopic and microscopic alteration in visceral organs viz., liver, kidney, lung, brain etc.

Petechial haemorrhages with moderate congestion, enlargement with pale and soft consistency was recorded in liver of rats of Group D and Group E receiving higher dose of deltamethrin whereas, only mild to moderate congestion with few petechial haemorrhages on parietal surface were found in rats of Group B and Group C. Histopathologically, Mild changes comprising of congestion and vacuolation in hepatocytes with nuclei at border were observed in liver of Group B rats whereas focal congestion in parenchyma of liver was observed in Group C rats. Group D and E revealed sporadic degeneration of hepatocytes with cytoplasmic vacuolation, congestion, fatty degeneration, focal

mononuclear cells infiltration, dilation of sinusoids and pronounced with mild haemorrhage and central venous congestion. Dose dependent macroscopic and micropscopic changes were in conformity with the finding observed in deltamethrin toxicity in mice (Haratym-Maj *et al.*, 2006), in rats (Manna *et al.*, 2005), cypermethrin in rats (Yavasoglu *et al.*, 2006; Ahmed *et al.*, 1989; Shakori *et al.*, 1988 and Hend and Butterworth, 1977) alpha cypermethrin in rats (Manna *et al.*, 2004a and Manna *et al.*, 2004b) and fenvalerate in mice (Tapase *et al.*, 1994).

Grossly, kidneys showed discoloration and congestion with variable severity in rats receiving 15 mg/kg deltamethrin with and without vitamin E in Group D and E, whereas moderate congestion and haemorrhage were noticed in rat receiving 7.5 mg/kg deltamethrin with and without vitamin E supplementation (Group B and C). Microscopically, the mild to moderate degeneration and coagulative necrosis of tubular epithelium with mild to moderate intertubular haemorrhages were observed in lower dose group. While kidneys of Group-D and E rats were showed degenerative changes, moderate to severe vascular changes characterized by severe intertubular haemorrhage along with tubular degeneration, coagulative necrosis and sloughing of tubular epithelium. The findings of the this study correlate with previous observation made by Killian *et al.* (2007) in rats, Haratym-Maj *et al.* (2006) in mice, Manna *et al.*, (2005) in rats treated with deltamethrin, Luty *et al.* (2000) in mice, Manna *et al.* (2004a and 2004b) in rats treated with alpha-cypermethrin, Ahmed *et al.* (1989) in rats, Lakkawar *et al.* (2004) in rabbits treated with cypermethrin and Tapase *et al.* (1994) in mice treated with fenvalerate.

Macroscopic lesions in lung were mainly characterized by severe congestion in apical and diaphragmatic lobes, haemorrhage and emphysema in rats belonging to Groups D and Group E compared to lower dose group as well as control group. Microscopically, lungs of Group-B revealed moderate edema and congestion with lymphoid hyperplasia, Perivascular edema, whereas Group C showed moderate congestion, edema, peribronchiolar lymphoid hyperplasia with pulmonary emphysema characterized by distension and dilatation of alveoli and degeneration of bronchial epithelium. Group D rats revealed foamy macrophage accumulation surrounding bronchioles, sever congestion, edema, emphysema and perivascular infiltration of mononuclear cells fibrosis and thickening of alveolar septa whereas, Group E showed only severe congestion with emphysema. Similar findings were also observed by by Haratym-Maj *et al.* (2006) in mice, Erdogen *et al.* (2006), Manna *et al.* (2005), Coombs and Clark (1978) in rats intoxicated with deltamethrin, Luty *et al.* (2000) in mice, Manna *et al.* (2004a and 2004b) in rats treated with alpha-cypermethrin, Lakkawar *et al.* (2004) in rabbits, Ahmed *et al.* (1989) in rat and Tapase *et al.* (1994) in mice found similar changes in cypermethrin and fenvalerate, respectively.

Brain of rats receiving 15 mg/kg deltamethrin with and without vitamin E (Group D and E) revealed severe meningial congestion and edematous swelling, whereas rats receiving lower dose receiving 7.5 mg/kg deltamethrin with and without vitamin E (Group B and C) revealed mild congestion on cerebellum and cerebrum. Significant microscopic lesions were evident in brain of rats receiving 7.5 mg/kg deltamethrin with and without vitamin E (Group B and Group C) but of varying degree of severity. Cerebral vessels revealed moderate engorgement in brain substance, with mild neuronal degeneration. Group D and E revealed severe cerebellar congestion with moderate neuronal degeneration and also evident of focal area of necrosis and moderate morphological changes in perkinje neurons. The findings of the present study correlate with previous observation made by Manna *et al.* (2005), Husain *et al.* (1996) in rats treated with deltamethrin, Manna *et al.* (2004b) in alpha cypermethrin toxicity in rats, Sayim *et al.* (2005) in rats, Lakkawar *et al.* (2004) in rabbits, Ahmed *et al.* (1989) in rats treated with cypermethrin and Tapase *et al.* (1994) in mice treated with fenvalerate.

Rats of Group B and Group C had showed gross lesion of mild congestion, whereas

Group-D and E revealed severe congestion and haemorrhage in myocardium. Group B and C revealed moderate congestion in myocardium and degeneration of cardiac muscles. In group D and E all rats showed severe engorgement of blood vessels and haemorrhages between the cardiac muscles fiber bundles, fragmentation of myocardial muscle fiber and also evident of degeneration, and necrosis of myocardium. Haratym-Maj *et al.* (2006) in mice treated with deltamethrin, Lakkawar *et al.* (2004) in rabbits and Ahmed *et al.* (1989) in rats treated with cypermethrin also reported necrosis of myocardium, fragmentation of myocardial muscle fiber, congestion in myocardium and degeneration of cardiac muscles.

Macroscopically no gross pathological lesions were observed in any of the treatment groups except mild to moderate congestion and shrinkage. While microscopically, there was observed varying degree of vascular changes, mild congestion with depletion of lymphocyte at germinal center in Group B and C, whereas Group D and E revealed severe congestion, necrosis and destruction of lymphoid cells leading to rarefaction and depletion of lymphoid elements. Almost Similar finding have also been reported earlier by Haratym-Maj *et al.* (2006) in mice treated with deltamethrin, Lakkawar *et al.* (2004), Desi *et al.* (1986) in rabbits and Ahmed *et al.* (1989) in rats treated with cypermethrin as well as Tapase *et al.* (1994) in mice treated with fenvalerate. In the present investigation, depletion of lymphoid population of germinal center of spleen was probably attributed to cytotoxic action of deltamethrin on lymphocyte. Thus resulting lymphoid depletion in lymphoid organs of rats given graded level of inclusions lead to depression in humoral immunity.

Grossly no pathological lesions were observed in any of the treatment groups except testes of all Groups showing mild to moderate congestion with engorged blood vessels as compared to control. Histopathological lesions in Group B and C showing moderate congestion and edematous fluid between seminiferous tubules. Group-D revealed severe congestion and edematous fluid between interseminiferous tubules whereas, Group E Showed emptying of seminiferous tubules and mild vacuolation, degeneration, cystic dilatation and coagulative necrosis of seminiferous tubules was a significant alteration in testes. The lesions observed in the present study were in conformity with the findings of Manna *et al.* (2005), Anderson *et al.* (2002) in deltamethrin treated rats, Manna *et al.* (2004a and 2004b) in alpha-cypermethrin treated rats, as well as Lakkawar *et al.* (2004) and Ahmed *et al.* (1989) in rats treated with cypermethrin.

The stomach of Group D and E rats was found slightly bloated and gastric mucosa was found moderately hyperemic. No appreciable gross lesions were observed in Group B and Group C rats. The microscopic changes in Group B and Group D rats revealed sub mucosal congestion as evident by engorged blood vessels in the mucosa. Similar findings were also found in Group C and Group E but of lesser severity, frequency and distribution. Almost similar pathological changes were reported by Manna *et al.* (2005), Coombs and Clark (1978) in deltamethrin treated rats, Manna *et al.* (2004a) in rats treated with alpha-cypermethrin and Lakkawar *et al.* (2004) in rats treated with cypermethrin.

The gross pathomorphological lesion observed in rats of all groups was only mild to moderate serosal congestion. Microscopically lesion include severe sub mucosal haemorrhages, denudation of intestinal villi, degeneration of glandular epithelium, infiltration of mononuclear cells in the underlying sub mucosa, and hypercellularity of goblet cells of intestine in rats of Group D receiving 15 mg/kg deltamethrin while, Group E rats reveled severe sub mucosal congestion along with scattered haemorrhages, decreased in height of villi with degenerative changes and blunt villi, whereas Group B and C showed mild congestion haemorrhages and slight decrease in height of intestinal villi. Almost similar pathological changes were reported by Coombs and Clark (1978) in deltamethrin treated rats and Lakkawar *et al.* (2004) in rats treated with cypermethrin.

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