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Assessment of Permethrin Toxicity Following Subacute Dermal Exposure in Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Permethrin is an insecticide in the pyrethroid family, used for control of pests in veterinary and agriculture sector. Present study was planned to evaluate the toxicity of permethrin following daily dermal application in Albino rats for 28 days. Thirty six rats were divided in to three groups, each group containing six animals. Group I was treated as control and rats in groups II and III were dermally exposed to permethrin at dose 100 and 200 mg.kg-1 b.wt., respectively daily for 28 days. Hematological and biochemical parameters were assessed at 0, 14th and 28th day of exposure. Significant changes in level of haemoglobin, total erythrocyte count and packed cell volume was observed at both the doses of permethrin during exposure period. The present investigation also resulted in significant elevation in aspartate amino transaminase, alanine amino transaminase, alkaline phosphatase, lactate dehydrogenase activities and significant increase in blood urea nitrogen and creatinine level in permethrin treated rats at both dose levels which indicated liver and kidney. Present study suggests that permethrin may be harmful when repeated dermal exposure occurs.

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1. INTRODUCTION

A pesticide is any chemical that is used to control, eradicate, or repel a particular species of plant or animal that is considered a pest. Insecticides are of chemical and biological origins, that are used to control a variety of pests. These chemical compounds are used in a variety of sectors like food, forestry, veterinary, agriculture and aquaculture [1]. Additionally, they are employed in the management of disease-transmitting vectors, including ticks and mosquitoes [2]. Because of their numerous uses and associated consequences, pesticides have gained attention of researchers. The need for pesticide products and their contribution to agricultural efficiency are evident, but the volume of manufacturing suggests that there is a significant risk of inadvertent exposure and misapplication. On one side, pesticides are beneficial for increasing crop yield and play important role in vector/pest control program but, on the other side, it has resulted in the manifestation of several health related issues in man and animals.

Synthetic pyrethroids are derived from natural pyrethrins found in *Chrysanthemum cinerariaefolium* plants. Synthetic pyrethroid pesticides are extensively employed in the fields of public health, veterinary medicine, and agriculture to control a variety of insect pests. Permethrin primarily affects nervous systems of insects and act as a neurotoxic. Interaction with sodium channels and the development of sustained depolarization in neurons are the mechanisms by which pyrethroids act. This results in recurrent nerve impulses that eventually cause paralysis and death [3-5].

Toxicity of insecticides in man, animal and aquatic organism may occur through oral, inhalation and dermal route. Many oral/dermal toxicity studies have been performed for different pyrethroids insecticides in the past by different scientists [5-8]. Nevertheless, the impact of repeated dermal exposure to permethrin on hemato-biochemistry has not been conducted yet. Therefore, present study was aimed to evaluate the dermal toxicity of permethrin in rats following subacute exposure.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Male Wistar albino rats (6-8 weeks) weighing 150-200 (g) were used for the experiment. Rats were housed under normal environmental conditions of temperature and humidity and 2 weeks before starting the experiment, they were allowed to adapt to the new environment. Animal rooms (23±2°C) with a relative humidity of 45.0 (±15) % was maintained on a 12:12 h light/dark photoperiod. Animals were provided with food with free access standard pellet diet and water *ad libitum*. Eighteen rats were divided into three groups, each having six animals.

2.2 Dose and Administration

Acute dermal LD_{50} of both permethrin is more than 2000 $mg.kg^{-1}$b.wt. in rats [9]. Therefore, $1/10^{th}$ dose of 2000 $mg.kg^{-1}$b.wt. (200 $mg.kg^{-1}$b.wt.) and $1/20^{th}$ dose of 2000 $mg.kg^{-1}$b.wt.(100 $mg.kg^{-1}$b.wt.) was selected for sub-acute toxicity study of permethrin following topical application.

Fur was removed around 24 hours prior to the test from each animal. Shaving on the dorsal portion of their trunks from the scapulae to the ilium wing, extending the lateral midline on either side was made, to cover the 10% area of body surface [10]. Afterwards, the animals were shaved once a week without suffering any skin injuries. Over the course of the 28-day study period, the test substance was kept in contact with the skin using a porous gauze dressing that was secured with non-irritating tape. This allowed the gauze to be in place for at least 6 hours per day of exposure.

2.3 Collection of Blood Samples

Blood samples were collected at 0, 14^{th} and 28^{th} day of study period from medial canthus of rats of different groups with the help of 1ml tuberculin syringe in clean and dry vial which was coated with anticoagulant (EDTA) for estimation of hematological parameters, another vial without anticoagulant for biochemical parameters.

For hematology, about 1ml blood was collected in sterile vial containing anticoagulant EDTA @ 2mg/ml of blood and remaining 1ml of blood was collected in a centrifuge tube without anticoagulant for serum separation. Following

blood clotting, the vial was centrifuged for five minutes at 2000 rpm, collecting serum in a sterile vial that was stored at -20°C for biochemical analysis.

2.4 Behavioral Signs of Toxicity and Mortality

Behavioral signs of toxicity and mortality, if any will be recorded during study period.

2.5 Hematological Parameters

Estimation of various hematological parameters, Total erythrocyte count (TEC), Hemoglobin (Hb), Packed cell volume (PCV), Total leukocyte count (TLC), Erythrocyte sedimentation rate (ESR), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH) and Mean corpuscular hemoglobin concentration (MCHC), was carried out as per the method of [11].

2.6 Serum Biochemical Parameters

Estimation of Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN) and creatinine were determined as per the method of Teiz [12].

2.7 Experimental Design

Following acclimatization to the laboratory conditions, the animals were randomly divided into three groups, each having 6 animals and placed in individual cages. The groups were classified as follow:

Group I (**normal control group**): Rats treated with no any chemical, served as control.

Group II (**Permethrin treated group**): Rats applied with permethrin at dose rate of 100 $mg.kg^{-1}$ b.wt. dermally daily for 28 days.

Group III(Permethrin treated group): Rat applied with permethrin at dose rate 200 $mg.kg^{-1}$ b.wt. dermally daily for 28 days.

2.8 Statistical Analysis

The data was expressed as mean ± SE. After a one-way analysis of variance, the data were put through Tukey's test for post hoc analysis, with the significance level at $p<0.05$. The statistical software SPSS (Version 20.0) was used for all analyses.

3. RESULTS AND DISCUSSION

3.1 Behavioral Signs of Toxicity and Mortality

No any mortality or behavioral signs of toxicity were recorded in rats of all groups during dermal exposure to permethrin. No clinical and behavioral alterations were exhibited by rats dermally applied with 100 and 200 $mg.kg^{-1}$ b.wt. of alpha-cypermethrin [13]. Abbassy and Mossa [14] also did not observe any signs of toxicity or mortality when administered 25 mg. kg^{-1} b.wt. of cypermethrin orally in rats for 90 days.

3.2 Body Weight

Non-significant increase in body weight of rats was observed on 7^{th},14^{th} and 21^{st} day of study period but on 28^{th} day, body weight increased significantly ($P<0.05$) in control group compare to '0' day value. However, body weight of rats reduced significantly ($P<0.05$) on 21^{st} day of dermal application in groups II and III which differed non-significantly with values of body weight on 28^{th} day (Table 1).

Body weight dropped 21 days onwards in groups treated with permethrin at doses of 100 mg/kg-1 and 200 mg/kg-1 body weight. This could be because the insecticide causes oxidative stress, which inhibits rat growth. It could also be because there is an overall increase in lipid and protein degradation [15]. Similar results were recorded by Dar et al. [16] in rats dermally applied with bifenthrin at dose 45 $mg.kg^{-1}$ b.wt. for 30 days.

Table 1. Effect of repeated 28-days dermal exposure of permethrin on body weight (g) of rats

Groups	0 day	7^{th} day	14^{th} day	21^{st} day	28^{th} day
I	$141.73 \pm .43^{b}$	143.80 ± 2.86^{b}	146.68 ± 2.81^{ab}	$149.71 \pm .24^{ab}$	$152.66 \pm .37^{a}$
II	$157.01 \pm .66^{a}$	$153.61 \pm .42^{ab}$	150.63 ± 2.30^{ab}	148.31 ± 2.53^{b}	$146.73 \pm .83^{b}$
III	$140.48 \pm .44^{a}$	$137.51 \pm .58^{ab}$	133.66 ± 3.74^{ab}	130.58 ± 3.42^{b}	$128.03 \pm .21^{b}$

Mean values bearing common superscripts (a, b) within rows (within groups) did not differ significantly (P<0.05)

3.3 Hematological Parameters

A significant (P<0.05) variation in values of haemoglobin, PCV and TEC was observed in groups II and III on 28th day of dermal application of insecticides compare to '0' day values. The percent (%) decrease in mean values of haemoglobin on 28th day of exposure day when compared to '0' day in groups II and III was 11.7 and 21.5, respectively and the percent (%) decrease in mean values of packed cell volume on 28th day of dermal exposure as compared to '0' day in group II and III, was 13.1, 14.3, respectively. Similarly, percent (%) decrease in mean values of total erythrocyte count on 28th day as compared to '0' day in groups II, III was 13.1 and 22.6, respectively. The findings revealed significant changes in Hb, TEC and PCV values at both dose levels of permethrin compare to 0 day values (Table 2-4) However values of ESR, TLC, MCV, MCH and MCHC did not differ significantly at both doses. Permethrin's disruptive activity on erythropoietic tissue may have impaired the viability of the cells, leading to the decrease in TEC, Hb concentration, and PCV seen in this study. The synthesis of the hormone erythropoietin is a crucial element to take into account when there is reduction in TEC. This corresponds to the damage that permethrin causes to the kidneys [16]. Dar *et al.* (2012) also reported significant (P<0.05) decrease in Hb, PCV and TEC, when bifenthrin was administered dermally at dose 45 $mg.kg^{-1}$ b.wt. for 30 days in rats [7]. Basir *et al.* (2011) also reported significant (P<0.05) changes in hematological parameters when administered lambda-cyhalothrin in rabbit for seven days [17]. Similar results were observed when rats were treated with 50 $mg.kg^{-1}$ b.wt. of cypermethrin orally for six weeks [8].

3.4 Biochemical Parameters

3.4.1 Liver function biomarkers

Values of AST, ALT ALP and LDH in control group did not vary significantly (P<0.05) at 0, 14th and 28th days compare to '0' day. Activity of AST, significantly (P<0.05) increased in groups II, III on 14th and 28th day of exposure compare to '0' day. The percent decrease in mean values of aspartate aminotransferase on 28th day as compared to '0' day, in groups II and III was 31.9 and 41.9, respectively (Table 5).

Table 2. Effect of repeated 28-days dermal application of permethrin on haemoglobin (g/dl) in rats of different groups (n=6)

Groups	0 day	14th day	28th day	Percent decrease
I	13.16 ± 0.33[a]	12.75 ± 0.38[a]	12.83 ± 0.35[a]	-
II	12.75 ± 0.38[a]	12.50 ± 0.28[a]	11.25 ± 0.48[b]	11.7
III	13.58 ± 0.23[a]	12.91 ± 0.23[a]	10.65 ± 0.55[b]	21.5

Mean values bearing common superscripts (a, b) within rows (within groups) did not differ significantly (P<0.05)

Table 3. Effect of repeated 28-days dermal application of permethrin on Packed cell volume (%) in rats of different groups (n=6)

Groups	0 day	14th day	28th day	Percent decrease
I	42.10 ± 1.82[a]	41.83 ± 1.98[a]	39.18 ± 2.30[a]	-
II	46.10 ± 2.66[a]	44.28 ± 1.70[a]	40.05 ± 1.11[b]	13.1
III	38.65 ± 1.68[a]	36.83 ± 1.43[a]	33.11 ± 1.14[b]	14.3

Mean values bearing common superscripts (a, b) within rows (within groups) did not differ significantly (P<0.05)

Table 4. Effect of repeated 28-days dermal application of permethrin on Total erythrocyte count (10^6/µl) in rats of different groups (n=6)

Groups	0 day	14th day	28th day	Percent decrease
I	7.48 ± 0.18[a]	7.11 ± 0.09[a]	7.16 ± 0.22[a]	-
II	7.96 ± 0.36[a]	7.70 ± 0.21[a]	6.91 ± 0.14[b]	13.1

III	7.90 ± 0.17[a]	7.13 ± 0.21[a]	6.11 ± 0.15[c]	22.6

Mean values bearing common superscripts (a, b, c) within rows (within groups) did not differ significantly (P<0.05)

Table 5. Effect of repeated 28-days dermal application of permethrin on Aspartate aminotransferase (IU/L) in rats of different groups (n=6)

Groups	0 day	14th day	28th day	Percent increase
I	52.53 ± 1.98[a]	50.38±2.58[a]	50.66 ± 1.14[a]	-
II	53.45 ± 1.93[c]	60.96±2.13[b]	70.51 ± 1.62[a]	31.9
III	53.06 ± 2.82[c]	62.18±1.39[b]	75.30 ± 2.06[a]	41.9

Mean values bearing common superscripts (a, b, c) within rows (within groups) did not differ significantly (P<0.05)

ALT level was significantly (P<0.05) increased in group III on 14th and 28th day compare to '0' day and the values differed significantly (P<0.05) in group II on 28th day of exposure compare to 0' day values. The percent increase in mean values of alanine aminotransferase on 28th day as compared to '0' day in group II and III was 18.4 and 35.1, respectively (Table 6).

The activity of ALP, significantly (P<0.05) increased in groups II, III on 14th and 28th day of exposure compare to '0' day values. The percent increase in mean values of alkaline phosphatase on 28th day as compared to '0' day in groups II and III was, 34.7 and 56.4, respectively (Table 7).

The activity of LDH, significantly (P<0.05) increased in groups II, III on 14th and 28th day of exposure compare to '0' day values. The percent increase in mean values of lactate dehydrogenase on 28th days as compared to '0' day in groups II and III was 12.6 and 18.6, respectively (Table 8).

The results of the present study indicate that permethrin induced liver damage at selected doses (100 $mg.kg^{-1}$ b.wt. and 200 $mg.kg^{-1}$ b.wt.) when applied dermally daily for 28 days, as shown by significant (P<0.05) increase in serum marker enzymes AST, ALT, ALP and LDH and the effect was dose dependent. A significant (P<0.05) increase in AST and ALT activities in rabbit administered with 8 $mg.kg^{-1}$ b.wt. of lambda-cyhalothrin for seven days orally, was reported by Basir *et al.* (2011). In different studies also pyrethroids induced significant increase in AST, ALT, ALP and LDH activities [5,7,14,18].

Table 6. Effect of repeated 28-days dermal application permethrin on Alanine aminotransferase (IU/L) in rats of different groups (n=6)

Groups	0 day	14th day	28th day	Percent increase
I	37.65 ± 1.24[a]	38.48 ± 1.53[a]	38.31 ± 0.97[a]	-
II	39.58 ± 1.07[b]	42.96 ± 0.72[b]	46.88 ± 2.71[a]	18.4
III	36.45 ± 1.75[c]	44.91 ± 1.64[b]	49.28 ± 1.45[a]	35.1

Mean values bearing common superscripts (a, b, c) within rows (within groups) did not differ significantly (P<0.05)

Table 7. Effect of repeated 28-days dermal application of permethrin on Alkaline phosphatase (IU/L) in rats of different groups (n=6)

Groups	0 day	14th day	28th day	Percent increase
I	48.93 ± 1.95[a]	50.16 ± 1.21[a]	51.65 ± 2.49[a]	-
II	50.45 ± 3.23[c]	57.15 ± 2.15[b]	67.98 ± 2.11[a]	34.7
III	49.28 ± 1.08[c]	60.41 ± 1.71[b]	77.08 ± 2.11[a]	56.4

Mean values bearing common superscripts (a, b, c) within rows (within groups) did not differ significantly (P<0.05)

Table 8. Effect of repeated 28-days dermal application of permethrin on Lactate dehydrogenase (IU/L) in rats of different groups (n=6)

Groups	0 day	14th day	28th day	Percent increase
I	214.08 ± 1.78[a]	215.05 ± 2.40[a]	211.46 ± 1.44[a]	-

II	207.43 ± 1.25^{c}	214.11 ± 1.38^{b}	233.73 ± 2.93^{a}	12.6
III	207.03 ± 1.37^{c}	219.63 ± 1.06^{b}	245.61 ± 3.24^{a}	18.6

Mean values bearing common superscripts (a, b, c) within rows (within groups) did not differ significantly (P<0.05)

Table 9. Effect of repeated 28-days dermal application of permethrin on blood urea nitrogen (mg/dl) in rats of different groups (n=6)

Groups	0 day	14th day	28th day	Percent increase
I	35.83 ± 1.19^{a}	35.81 ± 1.31^{a}	36.03 ± 1.11^{a}	-
II	35.65 ± 1.21^{b}	38.93 ± 1.24^{ab}	42.20 ± 1.34^{a}	18.3
III	36.81 ± 1.19^{b}	38.61 ± 1.30^{b}	46.71 ± 1.20^{a}	26.8

Mean values bearing common superscripts (a, b) within rows (within groups) did not differ significantly (P<0.05)

Table 10. Effect of repeated 28-days dermal application of permethrin on creatinine (mg/dl) in rats of different groups (n=6)

Groups	0 day	14th day	28th day	Percent increase
I	1.03 ± 0.05^{a}	1.08 ± 0.06^{a}	0.97 ± 0.02^{a}	-
II	0.92 ± 0.04^{b}	1.09 ± 0.05^{a}	1.20 ± 0.02^{a}	30.4
III	1.06 ± 0.04^{c}	1.20 ± 0.05^{b}	1.52 ± 0.12^{a}	43.3

Mean values bearing common superscripts (a, b, c) within rows (within groups) did not differ significantly (P<0.05)

The liver sustains the most damage since it is the first organ to come into contact with any foreign molecules that enter the body through the portal circulation. The primary markers utilized in the evaluation of liver injury are AST, ALT, ALP, and LDH. Transaminases, specifically AST and ALT, are used as particular markers for liver damage and are in charge of metabolic activities, detoxification procedures, and the production of energetic macromolecules for various vital functions. These enzymes may be overexpressed because of liver disease, disruptions in their production, and changes in the permeability of the liver membrane. As an enzyme specific to the liver, ALT activity is increased in response to severe liver damage caused by the generation of free radicals and hepatocyte degenerative changes brought on by pyrethroid metabolism [17]. Hepatocelluar necrosis and enzyme leakage into the blood may be the cause of the elevated LDH activity [19,20]. ALP assays can be used to determine the prognosis of lung and liver disorders. The cytoplasmic marker enzyme, or ALP, is a recognized marker of toxicity-induced cell and tissue damage [21].

3.4.2 Kidney function biomarkers

The values of BUN and creatinine in control group varied non-significantly at 14th and 28th day compare to '0' day. BUN level was significantly (P<0.05) increased at 28th day compare to '0' day in group II and III. The percent (%) increase in mean values of blood urea nitrogen on 28th day as compared to '0' day in groups II and III was 18.3 and 26.8, respectively (Table 9).

Creatinine level was significantly (P<0.05) increased in group III, on 14th and 28th day of exposure, compare to '0' day, but in group II significant (P<0.05) increase in creatinine level was recorded on 14th day which differed non significantly with values on 28th day. The percent (%) increase in mean values of creatinine on 28th day as compared to 0th day in groups II and III was 30.4 and 43.3, respectively (Table10).

The results revealed renal damage by permethrin, as evident from significant (P<0.05) elevation of BUN and creatinine level. Abbassy and Mossa, (2012) obtained significant (P<0.05) increase in BUN and creatinine level when administered cypermethrin at dose 25 mg.kg^{-1} b.wt. orally for 90 days in rats.

Urea is the end product of deamination of amino acids in the liver, which is a nitrogenous waste product. It is excreted in the urine [22]. Increased level of urea in blood is correlated with increased catabolism of protein in mammalian body. Increased synthesis of enzyme involved in urea production may results in more efficient conversion of ammonia to urea [14]. Creatine is metabolized to creatinine that is excreted completely in urine via glomerular filtration. Elevation in plasma creatinine and BUN levels may indicate renal damage, which may be attributed to urinary obstruction, which exacerbates decreased secretion of urea from the body [16]

4. CONCLUSION

The findings of present investigation suggest that during long term dermal exposure, permethrin may produce adverse effect at selected doses. Permethrin may be toxic to bone marrow as evidenced by decrease in hematological parameters during exposure period and may impair liver and kidney function, supported by significant changes in biochemical data. So, it can be concluded that permethrin is harmful at selected doses when applied dermally for 28 days. A great care should be taken during application of permethrin in agriculture, veterinary, household sectors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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