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SHORT TERM (21 DAYS) TOXIC IMPLICATIONS OF PERMETHRIN ON REPRODUCTIVE TISSUES OF MALE SWISS ALBINO MICE

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ABSTRACT: Permethrin, a member of one of the newest class of insecticides, the synthetic type-I pyrethroids, is very much in use nowadays. Due to its relatively low mammalian toxicity and high photostability, it has earned great popularity. Several reports suggest its endocrine disrupting activity, damaging effect on nervous system, its receptors, and other adverse effects. However, very limited information is available regarding its effect on reproductive organs. It is, therefore, imperative to bridge these lacunae. Hence, the present study was aimed to evaluate the effects of Permethrin on the reproductive tissues of male mice. Permethrin (130 mg/kg body weight) was administered orally for a period of 21 days. Biochemical parameters were assayed in testis, caput epididymis, cauda epididymis, seminal vesicle, and vas deferens of Swiss albino mice. The results showed that Permethrin administration lowered the gravimetric indices and decreased the levels of enzymes involved in the energy metabolism like ATPase, ALKPase, ACPase, and SDH, which may lead to oxidative stress and hamper the overall physiological functions.

INTRODUCTION: Bioactive substances derived or extracted from plants, animals, or microbes provide a valuable source which has been sparingly exploited as synthetic models or as actual pesticides [1]. Synthetic pyrethroids being a new class of agricultural insecticides, have captured the market with their wide potential to control insect pests. Synthetic pyrethroid insecticides are derivatives of the natural insecticidal pyrethrins found in the chrysanthemum.

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There has been a constant increase in the use of agricultural chemicals like pesticides to preserve the standing crops from the attack of pests and to boost up crop protection in order to meet the ever-increasing food demand of the rising human population [2, 3, 4]. However, the widespread use of pesticides in the public health sector and agriculture has resulted in environmental pollution with potential health hazards.

Permethrin,3-phenoxybenzyl (±) -cis, trans 3 -(2, 2-dichlorovinyl) -2, 2-dimethylcyclo -propane-1-carboxylate, is a synthetic analog of pyrethrin obtained from chrysanthemum plant and used extensively in agriculture to control lepidopterous pests on cotton and a variety of other crops. It is commercially used on a wide scale in aerosol sprays formulations and in the treatment of lice and

scabies infections. Besides, it is also used as a pest repellent in the army battle uniforms. It has low acute oral mammalian toxicity, a property often attributed to the rapid detoxification by metabolism [5]. Although considered safe, previous reports are available revealing that Permethrin administration caused genotoxic effects [6], malformations in the fetus of rodents following repeated exposure [7], and Permethrin toxicity with oral doses [8]. In addition, accidental and occupational human exposures by dermal contact have caused acute poisoning [9]. Permethrin has also been reported for its anti-estrogenic activity [10]. Disruption of voltage-gated sodium channels in both insect and mammalian neurons have been reported after pyrethroid treatment [11]. Moreover, Permethrin has been reported to demonstrate neurotoxic potential, which includes tremors in coordination, hyper-activity, increase activity like chewing, aggressive behaviors, resistance to been capture, and disruption in learning [12]. Keeping in view the available literature, the wide use of Permethrin in modern agriculture and relatively limited information regarding its effect on reproductive tissues, especially in mammals, demands further evaluation of the said pesticide. The present study is therefore undertaken to gauge the effect of Permethrin on reproductive tissues in rodent model *i.e.*, Swiss albino mice for a duration of 21 days.

MATERIALS AND METHODS:

Animals: Healthy adult male albino mice, Mus musculus of Swiss strain weighing between 30 and 35 gm, were obtained from Cadila Pharmaceuticals, Dholka, and Gujarat, India. All the animals were acclimatized for 7 days prior to the commencement of treatment and were maintained under the controlled condition with 12-h light and 12-h dark cycles at a temperature of 26 °C ± 2 °C and relative humidity of 30% to 70%. They were divided into 3 groups (A, B, and C) of 6 mice each. The animals were fed on a commercial pellet supplied by Amrut mice feed (Pranav Agro Industries, Vadodara, Gujarat, India) and ad water libitum. Experiments were conducted in accordance with the guidelines set by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India, and experimental protocols were approved by the institutional animals' ethics committee (167/GO/ReBi/S/99/CPCSEA).

Experimental Design:

TABLE 1: THE ANIMALS WERE DIVIDED INTO FOLLOWING GROUPS

Groups	Treatment and dose	Duration (days)	Day of autopsy
Group I	Control (untreated)	-	Sacrificed along with scheduled treated animals
Group II	Vehicle	21	22nd of post-treatment
Group III	Permethrin (PER)	21	22nd of post-treatment

(N = 6 animals/group)

Toxicant and Dose Selection: The increasing use of pyrethroid pesticides such as permethrin, in recent years has demanded the necessity to evaluate its reproductive toxicity.

Technical grade Permethrin of 95% purity was procured nanjing essence fine chemicals, China. Permethrin was dissolved in corn oil and administered *via* oral gavage at dose concentrations (130 mg /kg body weight).

The dose was determined on the basis of LD_{50} of Permethrin in corn oil, *i.e.*, 650 mg/kg body weight [13]. All other chemicals used in different assays were procured from HiMedia or Merck. All the groups were treated for 21 days, and at the end of the experiment, animals were weighed and euthanized using light ether anesthesia.

Tissue Collection: At the termination of the experiment, animals were dissected, and testis and other accessory reproductive tissues *viz.*, caput epididymis, cauda epididymis, vas deferens, and seminal vesicle were dissected out carefully. Tissues were weighed, processed, and homogenates were prepared accordingly.

Parameters Studied:

Body and Organ Weight: The body weight of control and all treated groups of mice were recorded to the nearest milligram on a digital balance (Reptech). The animals were weighed before and at the end of each week prior to autopsy. Similarly, weights of organs were recorded to the nearest milligram on digital balance (Aczet).

Total Protein: Protein estimation was done using standard protocol of Lowry et al. (1951) [14]. Color development was read at 540 nm in systronics digital spectrophotometer 167 against blank.

Succinate Dehydrogenase (SDH): SDH activity was measured by the method of Beatty *et al*. (1966) [15]. The electrons released by the enzyme SDH from the substrate are taken up by an electron acceptor INT which is reduced to red-colored formazan. After extracting it in ethyl acetate the color intensity was measured at 420 nm against blank. SDH activity was expressed as µg formazan formed / 15 min/mg tissue weight.

Adenosine Triphosphatase (ATPase): The ATPase activity of control and all treated groups of animals was assayed by the method of Quinn and White (1968) [16,] while inorganic phosphate liberated was estimated using the method of Fiske and Subbarow (1925) [17]. Readings were taken at 660 nm on a systronics digital spectrophotometer 167.

Alkaline Phosphatase (ALPase): ALPase activity was determined by the method of Bessey *et al*., (1946) [18]. The enzyme ALPase hydrolyses the substrate p-nitrophenyl phosphate into inorganic phosphate and p-nitrophenol.

The quantity of p-nitrophenol released under standardised conditions was measured at 410 nm. Enzyme activity was expressed as µ moles p-nitro phenol released / 30 min/mg protein.

Acid Phosphatase (ACPase): Activity of ACPase was determined by the method of Bessey *et al.* (1946) [18]. ACPase catalyzes hydrolysis of p-nitro-phenol at pH 4.8, liberating paranitrophenol and inorganic phosphate.

The liberated p-nitrophenol combines with NaOH to form a yellow colored complex which is measured at 420 nm and is directly proportional to the enzyme activity. Enzyme activity was expressed as µ moles of p-nitrophenol released/30 min/mg protein.

Statistical Analysis: For each parameter, a minimum of 6 replicates were done, and the results were expressed as Mean ± Standard Error (S. E.).

The data was statistically analyzed by Analysis of Variance (One way ordinary - ANOVA) by GraphPad Prism 8.0 software. Vehicle treated and Permethrin treated groups were compared with the control group.

RESULTS: The present investigation revealed non-significant changes in the control and vehicle groups of all the parameters studied.

Gravimetric Parameters:

Body Weight: Significant reduction ($p<0.002$) was recorded in the treated group (Group III) when compared to the control group I **Table 1**.

Organ Weight: Non-significant changes in weights of the testis, seminal vesicle, vas deferens, epididymis were observed in vehicle control (Group II) when compared to control (Group I).

Significant decline ($p < 0.001$) was seen in organ weights of testis, seminal vesicle and vas deferens ; weight of caput epididymis was also observed to significantly decrease ($p < 0.033$) and that of cauda epididymis reduced non-significantly after administration of toxicant for 21 days in Permethrin treated (Group III) when compared to control (Group I) **Table 2.**

Total Protein: Protein content in Testis, Seminal vesicle, and Vas deferens were observed to be non-significantly reduced in vehicle control (Group II) while showed a significant decline ($p < 0.001$) in total protein content of all the organs studied in the treated group (Group III) when compared to control (Group I) **Table 3**.

Succinate Dehydrogenase (SDH): After 21 days of treatment, non-significant changes in SDH activity of testis was noticed in Group II (vehicle control); however, a significant reduction ($p< 0.002$) was seen in Group III (Permethrin treated), when compared to Group I (control I) **Table 4**.

Adenosine Triphosphatase (ATPase): ATPase activity in testis changed non-significantly in vehicle control (Group II), while significant depletion ($p<0.001$) was observed in PER administered animals (Group III) after 21 days, when compared to Group I **Table 5**.

Alkaline Phosphatase (ALPase): ALPase activity in testis of treated mice for 21 days showed a non-significant depletion in group II (Vehicle control)

however, a significant reduction ($p<0.001$) was observed in (Group III), when compared to control (Group I) **Table 6**.

Acid Phosphatase (ACPase): Non-significant changes in ACPase activity were observed in the vehicle group (Group II).

However, a significant increase ($p<0.001$) was observed in the testis of Permethrin administered group (Group III), when compared to Group I after 21 days **Table 7**.

TABLE 1: BODY WEIGHT (gm) IN CONTROL, VEHICLE AND TREATED MICE AFTER 21 DAYS

Groups	Duration (21 Days)
Control (Group I)	37.00 ± 0.966
Vehicle (Group II)	36.67 ± 0.843^{ns}
PER treated group (Group III)	32.17 ± 0.654**

N=6, values are represented as Mean ± S. E. * p<0.033, ** p<0.002, ***p<0.001, ns–non-significant. Analysis of variance at p<0.05 level

TABLE 2: ORGAN WEIGHTS (mg) OF CONTROL, VEHICLE AND TREATED MICE AFTER 21 DAYS

Groups	Duration (21 Days)				
	Testis	Caput epididymis	Cauda epididymis	Vas deferens	Seminal vesicle
Control (Group I)	313.9 ± 4.796	45.7 ± 5.021	30.62 ± 1.143	41.02 ± 0.621	322.1 ± 6.17
Vehicle (Group II)	313.4 ± 5.069 ^{ns}	50.28 ± 0.818 ^{ns}	30.78 ± 0.671 ^{ns}	40.76 ± 0.734 ^{ns}	316.1 ± 6.49 ^{ns}
PER treated group (Group III)	235.7 ± 11.98***	34.8 ± 0.887*	28.2 ± 1.283 ^{ns}	29.34 ± 1.573 ***	202.6 ±14.41 ***

N=6, values are represented as Mean ± S. E. * p<0.033, ** p<0.002, ***p<0.001, ns – non-significant. Analysis of variance at p<0.05 level

TABLE 3: TOTAL PROTEIN CONCENTRATION (Mg/100 mg TISSUE WEIGHT) TESTIS, SEMINAL VESICLE, VAS DEFERNS OF CONTROL, VEHICLE AND TREATED MICE AFTER 21 DAYS

Groups	Duration (21 Days)		
	Testis	Seminal vesicle	Vas deferens
Control (Group I)	9.275 ± 0.063	20.56 ± 0.017	16.74 ± 0.149
Vehicle (Group II)	9.377 ± 0.046^{ns}	20.41 ± 0.080^{ns}	16.96 ± 0.077^{ns}
PER treated group (Group III)	3.643 ± 0.071***	10.49 ± 0.065***	12.57 ± 0.059***

N= 6, values are represented as Mean ± S.E. * p<0.033, ** p<0.002, ***p<0.001, ns–non-significant. Analysis of variance at p<0.05 level

TABLE 4: SDH ACTIVITY (mg FORMAZAN RELEASED/ 15 min / mg PROTEIN) IN TESTIS OF CONTROL, VEHICLE AND TREATED MICE AFTER 21 DAYS

Groups	Duration (21 Days)
	Testis
Control (Group I)	151.2 ± 3.808
Vehicle (Group II)	150.5 ± 3.765 ^{ns}
PER treated group (Group III)	132.8 ± 1.487 **

N=6, values are represented as Mean ± S. E. * p<0.033, ** p<0.002, ***p<0.001, ns–non-significant. Analysis of variance at p<0.05 level

TABLE 5: ATPASE ACTIVITY (µm OF INORGANIC PHOSPHATE RELEASED / 30 Min / Mg PROTEIN) IN TESTIS OF CONTROL, VEHICLE AND TREATED MICE AFTER 21 DAYS

Groups	Duration (21 Days)
	Testis
Control (Group I)	11.95 ± 0.177
Vehicle (Group II)	11.93 ± 0.178^{ns}
PER treated group (Group III)	7.645 ± 0.084 ***

N=6, values are represented as Mean ± S. E. * p<0.033, ** p<0.002, ***p<0.001, ns–non-significant. Analysis of variance at p<0.05 level

TABLE 6: ALPASE ACTIVITY (mm OF P-NITRO PHENOL RELEASED/ 30 Min/ Mg PROTEIN) IN TESTIS OF CONTROL, VEHICLE AND TREATED MICE AFTER 21 DAYS

Groups	Duration (21 Days)
	Testis
Control (Group I)	2.792 ± 0.108
Vehicle (Group II)	2.835 ± 0.090^{ns}
PER treated group (Group III)	1.74 ± 0.016***

N=6, values are represented as Mean ± S. E. * p<0.033, ** p<0.002, ***p<0.001, ns –non-significant. Analysis of variance at p<0.05 level

TABLE 7: ACPASE ACTIVITY (µm OF P-NITRO PHENOL RELEASED/ 30 Min/ Mg PROTEIN) IN TESTIS OF CONTROL, VEHICLE AND TREATED MICE AFTER 21 DAYS

Groups	Duration (21 Days)
	Testis
Control (Group I)	2.212 ± 0.014
Vehicle (Group II)	2.198 ± 0.009 ^{ns}
PER treated group (Group III)	8.502 ± 0.300***

N=6, Values are represented as Mean ± S. E. * p<0.033, ** p<0.002, ***p<0.001, ns–non-significant. Analysis of variance at p<0.05 level

DISCUSSION: Pesticides represent an important group of environmental pollutants [19] which can modify gene expression, changing protein synthesis in different tissues [20, 21]. The present investigation deals with the assessment of synthetic pyrethroid pesticide, Permethrin on various biochemical parameters and its effect on male reproductive and accessory organs, which is discussed further.

Oral administration of Permethrin to male Swiss albino mice caused a decrease in feed consumption; this hypophagia can be attributed to the decrease in metabolism or inhibition of hunger resulting in a lack of appetite or anorexia [22]. The present study also revealed a significant decline in the bodyweight of Permethrin administered animals as compared to the control. Monitoring body weight during treatment provides an index of the general health status of the animals, and such information is important for the interpretation of reproductive effects [23]. Ngoula *et al.* (2014) [24] also observed a similar reduction in body weight after Dimethoate insecticide treatment, while Zhang *et al.,* (2007) [25] showed a non-significant decrease in body weight of adult male mice when administered with a higher dose of cispermethrin for 6 weeks.

Besides, reports suggest that an increase or decrease in absolute or terminal body weight after treatment with any chemical is an indicator of the toxic effect of that particular toxicant [26]. Furthermore, the relative weight of testis, cauda epididymis, seminal vesicle, and vas deferens of Swiss albino male mice after 21 days duration also revealed a significant decline after Permethrin administration. Toxic effects of the test chemical/material have been conventionally co-related by comparing organ weights of treated and untreated groups of animals [27]. Similar results were obtained by Bal R *et al.,* (2012) [28], where imidacloprid (A neonicotinoid pesticide) affects the reproductive organ of male rats by decreasing the mass of accessory sex organs. A similar decline in the weight of reproductive organs was witnessed in female albino rats upon administration of Cypermethrin [29].

Testicular weight is a valuable index of reproductive toxicity in male animals [30]. A highly significant decline in the weight of testis was confirmed as compared to the control in the present investigation. This decline could be correlated with degeneration of germinal epithelium, disruption of spermatogenesis, or inadequate supply of testosterone [31, 32, 33]. The present study exhibited a low significant reduction in the weight of caput epididymis, while the cauda epididymis showed a non-significant decrease in the Permethrin administered group as compared to the control. Reduction in the weight of epididymis observed might be attributed to diminished testosterone level, reduced tubular size or decreased number of spermatozoa [34, 35].

The weight of vas deferens and seminal vesicle were lowered significantly in dose treated group as compared to the control. Reduction in weight of vas deferens reflected reduced sperm count and androgen level. Similar results were confirmed by Arena *et al.* (2008) [36] where testis and epididymis weight was decreased after 30 days exposure to Fenvalerate, a pyrethroid pesticide. The results of Desai *et al.,* (2016) [37] corroborate with our findings where the weight of testis, cauda epididymis, and seminal vesicle decreased upon administration of Deltamethrin after 45 days.

The present study revealed a highly significant decline in testis' protein content, vas deferens and seminal vesicle in the treated group compared to control. This reduction can be attributed to the reduction in secretory activity of the testis, disturbances in protein synthesis or reduction in the number of germ cells in testis [39, 40].

Similar results were obtained by Mukadam and Kulkarni (2014) [38] where Cypermethrin decreased the total protein content in male and female gonads of estuarine clam, Marcia opima. However, contradictory findings were noted by Joshi *et al.* (2011) [41], where a rise in total protein after administration of Cypermethrin for 21 days was observed.

The analysis of testicular enzymes acts as an important tool for the assessment of testicular growth and development in animals. A significant decline in the succinate dehydrogenase (SDH) activity in the testis was noted after 21 days of Permethrin treatment, indicating the possible disturbances in the testicular function of the treated animals. The similar, decline in SDH was recorded by Ksheerasagar and Kaliwal (2013) [42] after 30

days exposure to Carbosulfan in the testis of albino mice and in the rat testis after exposure of pesticide Quinalphos for 60 days [43]. These findings hence corroborate with our results. The adenosine triphosphatase (ATPase) activity in the testis was found to be significantly altered in the treated group after 21 days, which can be attributed to the impairment in the ATP generation mechanism at the cellular level.

Similar results have also been obtained by Shagirtha and Pari (2011) [44] who demonstrated that Cadmium exposure lowered the activity of ATPase enzyme in the testis of the treated rat.

Alkaline phosphatase (ALPase) activity in the testis of Swiss albino mice after treatment for 21 days showed a decline in the present investigation, which might be due to increased permeability of plasma membrane or cellular necrosis in treated animals [45]. The similar, decline in the activity of testicular alkaline phosphatase was observed in animals exposed to chromium [46], mercury [47] and stannous chloride [48]. The results of Joshi *et al.* (2005) [49] corroborate with our findings where the ALPase activity was found to be lowered after the administration of Mancozeb for 30 days in rat testis.

Acid phosphatase (ACPase) is a lysosomal enzyme which is used as a marker parameter of specific androgen dependent steps in spermatogenesis [50]. Results of the present study showed increase in ACPase activity in testis of the treated group after 21 days when compared to control. The increase in acid phosphatase activity can be interpreted as a shift of the tissue emphasis on energy break down pathway from normal ATPase system to phosphatase system [51].

Similar raise in ACPase activity was found by Mahgoub and El-Medany (2001) [52] and Choudhary N *et al.,* (2008) [53] when male rats were exposed to Methomyland Malathionfor 60 days respectively. Thus, ACPase activity was studied in the present investigation and was found to be elevated post 21 days of treatment.

The observed decline in various enzyme activities of the testicular tissue in the present investigation suggests that impairments at the cellular level like lowering of steroid genesis, impairment in ATP production, and mitochondrial function. Further, the analyses of testicular enzymes are an important tool for the assessment of testicular growth and development.

CONCLUSION: The obtained result throw striking observations that pesticides like Permethrin are not safe to mammalian tissues like reproductive tissue. These toxic effects in the long term can contribute to an increasing number of infertility cases. Furthermore, it demands additional ameliorative investigations which can benefit the society and thereby prevent reproductive damage. Our unpublished data also suggest toxicity of the Permethrin on other mammalian tissues too. Social awareness and strict implementation of regulatory laws, monitoring, and necessary preventative measures should be taken while handling pesticides.

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