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ORIGINAL ARTICLE

Fenvalerate Induced Genotoxicity in Mammals

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ABSTRACT
High insecticidal activity and low mammalian toxicity of fenvalerate (a synthetic pyrethroid) makes it a commonly used insecticide in agriculture. Oral LD_{50} of fenvalerate was determined by log-dose/probit regression line method, and found 426.58 mg/kg b.wt. In this study genotoxic effect of fenvalerate was analyzed by measuring chromosomal aberration (CA) in bone marrow of wistar rats. Rats were administered oral dose equivalent to LD_{25} for acute exposure (1 and 2 days) and dose equivalent to LD_5 to chronic exposure (15, 30 and 60 days) treatments. Controls were run simultaneously for each treatment.
Genotoxicity of fenvalerate has been found significant after acute (1and 2 days) and chronic (60 days) exposures, while non significant changes were observed after subacute (15 and 30 days) exposures. This mutagenic property of fenvalerate may be due to its ability to cause degenerative and necrotic damage to mammalian tissue.
Key words: *Genotoxicity, Fenvalerate, Chromosomal aberration, wistar rats, LD_{50}.*

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INTRODUCTION

Pesticide is a substance or a mixture used against pest in all forms. Pesticides play an important role in agriculture, particularly in controlling harmful pests and insects. In order to find a low mammalians toxicity, less insect resistance and low persistence, the number of group of insecticides have been synthesized, and synthetic pyrethroid is the result of one of such attempt [1]. To access the genetic damage induced by physical and chemical agent including pesticides, various test systems have been described in mammalian cell *in vitro* and *in vivo* and in plants [2]. The most reliable genotoxicity evaluation for mammals is test of chromosomal aberration. Albino rat is a member of largest mammalian order rodentia, so rat has been selected for the present study.
Fenvalerate a third generation synthetic pyrethroid insecticide [3], is active against a wide variety of pests. Fenvalerate has strong effect on mitotic spindle apparatus resulting in the occurrence of C mitosis found by Carbonell *et.al.*[4]. Ghosh *et.al.*[5] reported that fenvalerate treatment for 6,12 and 24 hr, a significant increase in CA was observed in albino mice. In the present study the induction of structural chromosomal aberration *in vivo* in rat bone marrow by fenvalerate has been investigated to confirm its genotoxicity.

MATERIALS AND METHODS

Wistar albino rats [*Rattus norvegicus* (Berkenhout)] have been selected from inbred colony. Healthy adult rats of almost equal size and weight (120±5) irrespective of sexes were selected randomly. The rats were maintained in polypropylene cages and acclimatized at temperature 25±5^{0}c, relative humidity 60±5% and a photoperiod of 12 hr/day. The rats were provided food and water *ad.libitum.*
Fenvalerate [(RS)-α-cyano-3-phenoxybenzyl (RS)-2-(4-chloro-phenyl)-3-methyl-butyrate] (93.2%) was provided in liquid form by Bharat Insecticides Ltd. New Delhi.
LD_{50} of fenvalerate has been estimated by log-dose/probit regression line method [6]. Clastogenesity has been assessed after acute (1 and 2 days), sub-chronic (15, 30 and 60 days) treatments. LD_{25} dose(367.3mg/kg b.wt.) was introduced orally through gavage tube for acute treatment, once and effect was observed after 24 hr and 48hr. LD_5 dose(305.5mg/kg b.wt.) was introduce for sub-chronic 60 days treatment and effect was observed after 15th , 30th and 60th days exposure. Ground nut oil was used as vehicle. Controls run for each treatment with same amount of vehicle *i.e.* ground nut oil. Recovery

assessment for acute and sub-chronic treatment was carried out by 7 and 45 days simultaneously. Rats were sacrificed by chloroform anesthesia.

Bone marrow was isolated from femur by the method proposed by Heddle [7]. Chromosomal aberration assay was done as described by Preston *et.al.*[8] incorporating cholchicine treatment, slide preparation through harvesting, hypotonic treatment, fixation and staining in giemsa. The metaphase scoring was done after acute (1 and 2 days) and sub-chronic (15, 30 and 60days) treatment exposures and 7 days acute and 45 days sub-chronic recovery. The chromosomal abnormalities were considered which includes chromosome and chromatid breaks and fragments of untraceable origin. Chromosome and chromatid gaps were also recorded but not included among aberration in the final evaluation. Percentage of aberration and frequency of aberrant cells have been calculated.

The experimental data were analyzed for mean value and standard error (mean ± SE) for all groups, and comparison made by one way parametric ANOVA and followed by HSD Tukey test.

RESULTS AND DISCUSSION

The rats of different experimental sets were treated with different conc. of fenvalerate and mortality number and percentage of rats for each dose were noted after 96 hours. The mortality percentage showed a corresponding increase with the increased dose of fenvalerate. The calculated value of LD_{50} for fenvalerate is 426.58 mg/kg body weight. The toxicity of fenvalerate was found to be dose dependent.

Table I. Chromosomal aberrations of bone marrow cells of wistar rats after acute and sub-chronic oral exposure of fenvalerate.

S. No.	Treatment	Dose (mg/kg b.w.)	No. of rats treated	Treat-ment time (In days)	No. of Cells / animal	Chromosomal aberration					Total			% of aberration without gap		Frequency of aberrant cell	
						Gap		Break		Fragments	Without Gap	With Gap	No of aberrant cell	Mean± S.E.	Significance	Mean± S.E.	Significance
						ct	cs	ct	cs								
1.	Control	-	5	01	250/5	1	0	1	0	1	2	3	2	0.80±0.65		0.008±0.006	
2.	Acute	LD_{25}	5	01	250/5	5	2	4	2	7	13	20	12	5.20±0.95	P<0.01↑	0.048±0.009	P<0.01↑
3.	Control	-	5	02	250/5	1	0	1	0	1	2	3	2	0.80±0.55		0.008±0.005	
4.	Acute	LD_{25}	5	02	250/5	4	3	4	2	5	11	18	10	4.40±0.66	P<0.01↑	0.040±0.006	P<0.01↑
5.	Control	-	5	7	250/5	1	0	0	1	1	2	3	2	0.80±0.56		0.008±0.005	
6.	Recovery*	-	5	7	250/5	1	0	1	1	2	4	5	3	1.60±0.35	P>0.05↑	0.012±0.003	P>0.05↑
7.	Control	-	5	15	250/5	0	0	1	0	1	2	2	2	0.80±0.44		0.008±0.004	
8.	Sub-chronic	LD_5	5	15	250/5	2	1	1	2	5	8	11	7	3.20±0.38	P<0.05↑	0.028±0.003	P<0.05↑
9.	Control	-	5	30	250/5	1	0	1	1	1	3	4	3	1.20±0.33		0.012±0.003	
10.	Sub-chronic	LD_5	5	30	250/5	2	2	1	1	3	5	9	5	2.20±0.48	P<0.05↑	0.020±0.004	P<0.05↑
11.	Control	-	5	60	250/5	1	0	2	1	1	4	5	4	1.60±0.65		0.016±0.006	
12.	Sub-chronic	LD_5	5	60	250/5	4	2	4	1	7	12	18	12	4.80±0.38	P<0.01↑	0.048±0.003	P<0.01↑
13.	Control	-	5	45	250/5	2	1	1	1	1	3	6	3	1.20±0.55		0.012±0.005	
14.	Recovery**	-	5	45	250/5	2	0	1	1	2	4	6	4	1.60±0.48	P>0.05↑	0.016±0.004	P>0.05↑

* Acute recovery- observed after seven days without dosing soon after acute dosing. ** Subchronic recovery- observation taken after 45 days without dosing soon after 60th day dosing.↑ Increased, ct Chromatid break, cs Chromosome break,

Percentage of aberrations (without gap) have been calculated and compared with their respective control value for significance level (table I). Increase in the percentage of aberration in the order of ($p<0.01$) after acute (1 and 2 days) and ($p<0.05$) after sub chronic (15, 30 and 60 days) treatments. A non significant ($p>0.05$) increase have been observed in the percentage of aberration after 7 and 45 days recovery.

Result of the present study reveals that fenvalerate caused significant increase of chromosomal aberration with compare to their control values in bone marrow of rats during acute and sub chronic treatment. Finding indicates *in vivo* clastogenic and spindle poisoning action of fenvalerate. The present finding is supported by previous report on clastogenic potential of synthetic pyrethroids as manifested in rodent bone marrow [10]. Pati and Bhunya reported chromosomal aberration in rats *in vivo* due to fenvalerate treatment [11].

This mutagenic property of fenvalerate may be due to its ability to cause degenerative and necrotic damage to mammalian tissue. Hydrolytic enzymes may release from damaged lysosome. These hydrolytic enzymes get entered in nucleus and may cause DNA damage by their digestive action inside nucleus which in turn leads to chromosomal aberration. The present study gain supported by Singh and Saxena[12].

Clastogenic property of fenvalerate has also been assessed after sub chronic dosing to reveal cumulative effect. Further recovery assessment is also observed for 7 days after acute treatment and 45 days after sub chronic treatment. Increase in percentage of chromosomal aberration has been found to be non significant ($p>0.05$). Pati and Bhunya observed magnitude of chromosomal aberration to be low in rat bone marrow after sub chronic treatment compared to acute treatment with fenvalerate [11]. The decrease in aberration frequency with recovery assessment is probably due to non availability of the critical concentration of genetically reactive metabolites of fenvalerate at the target DNA molecule. A critical concentration of reactive metabolites of chemical compound in the target tissue or cell is extremely important for the production of any mutation [13].

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