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Effect of repeated oral administration of lead and repeated dermal exposure of λ-cyhalothrin alone and in combination on the hematological parameters in goats

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Abstract
The present study was aimed to investigate the effect of lead and λ-cyhalothrin alone and in combination on different haematological parameters in goats. Sixteen healthy goats of either sex weighing 35-40 kg were divided in 4 groups (Group-A, B, C and D) with 4 goats in each group. Group-A goats were served as control. Group B goats were given lead-acetate @ 10 mg/kg B.W. (1/10 of LD_{50}) orally daily for 28 days. Group C goats were received five dermal-applications (on day 0, 7, 14, 21 and 28) of λ-cyhalothrin @ 2.25mg/kg B.W. whereas group-D goats co-exposed to both lead acetate and λ-cyhalothrin in at same dose and route as in group-B and C. A significant decrease in TEC, PCV and Hb values were found in group-B and C goats as compared to control group. However, in lead-acetate treated goats of group-B a significant increase in TLC while λ-cyhalothrin group-C goats a significant decrease in TLC was found as compared to control group. Also a significant decrease in osmotic fragility of erythrocytes by lead-acetate and a significant increase in osmotic fragility of erythrocytes by λ-cyhalothrin were induced as compared to control group. The changes produced in haematological parameters are indicating that both the agents alone and their co-administration may be involved in free radicals generation.

Keywords: biochemical parameters, haematological parameters, oxidative stress, lead-acetate, λ-cyhalothrin, goats

Introduction
Pesticides constitute an important class of compounds that are being used throughout the world for increasing agricultural production (Qin and kong, 2006) [34] and beneficial only if used judiciously. Its indiscriminate use even at recommended doses for long durations result in serious health hazards in almost every species including man and domestic animals (Abdollahi *et al*., 2004) [1]. Pyrethroids are being used as substitutes for organophosphates and organochlorines for the management of pest control because of their low persistency in environment and mammalian toxicity (Kale *et al*., 1999) [18]. They are also effective against a wide range of ectoparasites (lice, flies and ticks) on pets and livestock (Kale *et al*., 1999; Yadav *et al*., 2003) [18]. Chemically, pyrethroids are classified as type I and type II pyrethroids. Type I has basic cyclopropane carboxylic ester structure, no cyano-group (permethrin, allethrin) and produces tremor (T) syndrome while type II has an additional cyano-group at the benzylic carbon atom resulting in enhanced insecticidal activity (cypermethrin, cyhalothrin) and produces choreoathetosis/salivation (CS) syndrome.

Lambda-cyhalothrin (λ-cyhalothrin) is a type II pyrethroid used to control a wide range of pests. It consists of a pair of isomers of cyhalothrin and is more biologically active than cyhalothrin (IPCS, 1990). It accumulates in biological membranes leading to oxidative damage (Michelangeli *et al*., 1990) [25].

Heavy metals are among the most widespread potential chemical contaminants in the environment and are transferable to man and animals through diet and other routes (Pace and Iannucci, 1994) [30]. Lead the fifth most abundant metal in the world is a ubiquitous environmental contaminant due to its significant role in modern industry (Shalan *et al*., 2005) [37]. It is one of the most toxic metals known due to its wide ranging effects on multiple body systems (Pattee and Pain, 2003) [33] including neurological (Moreira *et al*., 2001) [26], immunological (Ercal *et al*., 2000) [10], cardiovascular, cerebro-vascular (Apostoli *et al*., 1990; Fanning *et al*., 1988) [4, 11], reproductive system (Alexaki *et al*., 1990) [3], renal (Loghman-Adham, 1997), hepatic and especially hematological dysfunctions (Patra and Swarup, 2000) [32].

In view of the dramatic and tremendous increase in the use of λ-cyhalothrin and ever increasing lead levels in different sources, simultaneous exposure of human and animals to these chemicals is a reality. Keeping this fact the present study was assigned.

Materials and Methods

The experimental study was conducted on adult goats of either sex, 3-4 years old, weighing 35-40 Kg and kept under standard managemental conditions. The animals were dewormed 20 days prior to the start of experiment and acclimatized to the experimental conditions for a period of 2 weeks. After acclimatization, adult goats were randomly divided into 4 groups (A, B, C & D) and each group comprises 4 animals. Group-A served as control whereas group-B animals were treated with lead acetate @ 10mg/Kg BW/day and drenched daily at around 9:00 AM for 28 days. In group-C, animals received 5 dermal-applications (On day 0, 7, 14, 21 & 28) of λ-cyhalothrin @ 2.25mg/kg BW directly onto the skin down the midline of the back (Knight *et al.*, 1987) [21] and group-D animals were exposed to both lead acetate and λ-cyhalothrin at same dose and route as in group-B and C (Table 1).

Blood samples were collected from all the animals by jugular veni-puncture on day 0 and 3, 7, 14, 21 and 28 days after the administration of lead acetate and λ-cyhalothrin. The blood samples were also collected on day 7 and 14 after termination of toxicant exposure period of 28 days. 2 ml of blood from each animal was kept in clean sterile plastic tubes containing dipotassium salt of EDTA as anticoagulant (Hi Media Mumbai, @ 2 mg/ml of blood).

Table 1: Showing the experimental design (groupings of goats and their respective treatment).

Groups(n=4)	Treatment	Dose & Route of administration	Exposure-period
A	Control	Tap water	28 days
B	Lead acetate	10mg/kg BW, Orally through drinking water	28 days
C	λ-cyhalothrin	2.25mg/kg BW, Dermal exposure	5 dermal-applications (On day 0, 7, 14, 21 & 28)
D	Lead acetate+ λ-cyhalothrin	10mg/Kg BW, Orally through drinking water+ 2.25mg/kg BW, Dermal exposure	28 days+ 5 dermal-applications (On day 0, 7, 14, 21 & 28)

Haematological Parameters

Tests	Methods
Haemoglobin	Gowenlock, 1966),
Packed Cell Volume	(Micro-haematocrit, 1987)
Total Leukocyte Count	(Benzamin, 1985)
Total Erythrocyte Count	(Benzamin, 1985)
Osmotic fragility of erythrocyte	Oyewale (1991).

Statistical analysis

A standard statistical procedure was followed. The data collected during the experiment was subjected to analysis of variance under completely randomized design (CRD) and the level of significance was tested using Duncan Multiple Range Test (Duncan, 1955) [9] at 5% ($P < 0.05$) level.

Results and Discussion

Haemoglobin, packed cell volume and total erythrocyte count

In both lead-acetate and λ-cyhalothrin treated-goats separately (group-B & C) and in combination treated-goats (group-D) a significant decrease in haemoglobin, packed cell volume and total erythrocyte count were found as compared to control goats (group-A) (Table 2, 3 &4) Similar significant decrease in erythrocyte count and haemoglobin level has also been reported by Ahrar *et al*. (2010) [2] and Dahamna *et al*. (2009) [8] in rabbits and rats exposed to λ-cyhalothrin for 14 days and 4 weeks, respectively. Whereas, Ibrahim *et al*. (2011) [16] and Ozsoy *et al*. (2011) [29] also reported a significant reduction in RBCs, PCV, Hb in rats exposed to lead acetate for 60 days. Although goats treated with a combination of lead-acetate and λ-cyhalothrin (group-D), induced a more significant decrease in haemoglobin, packed cell volume and total erythrocyte count as compared to when used separately (group-B & C). Similar finding has also been reported by Institoris *et al*. (2001) [17] in wistar rats repeatedly co-exposed to cypermethrin and lead for 28 days.

The lead induced haematological alterations may be due to the effect of lead on the activity of δ-aminolevulinic acid dehydratase (ALAD) and Ferrochelatase, are the key enzymes of heme-synthesis (Klassen, 2001) [20]. Moreover lead acetate also inhibits the conversion of coproporphyrinogen III to protoporphyrin IX leading to reduction in haemoglobin production and shortening the life span of erythrocytes (Klassen, 2001) [20]. Further, progressive destruction of RBCs due to binding of lead to RBC results in an increased fragility and destruction of these cells which could be another reason for decrease in haematological values (Rous, 2000) [35].

Pyrethroids exposure may results in formation of haemoglobin to methaemoglobin and Heinz bodies. The attachment of Heinz bodies to the plasma membrane increases membrane rigidity leading to increased RBC lysis or premature removal from circulation (Gosset, 2004) [13]. Moreover, pyrethroids also cause hemolysis, which ultimately leads to reduced RBC in circulation (Mandal *et al*., 1986). The decreased RBC counts in rats, co-administered lead-acetate and λ-cyhalothrin, could be due to reduced erythropoiesis or impaired biosynthesis of heme in bone marrow (Khan *et al*., 2009) [19].

Table 2: Showing the effect of Lead, λ-cyhalothrin, Lead + λ-cyhalothrin on Haemoglobin (g/dl) in goats (n=4).

Treated Group(s)	Treatment Period						Post Treatment Period	
	Zero day	3rd day	7th day	14th day	21st day	28th day	7th day	14th day
Group-A Control)	10.53 ± 0.12^{aA}	10.44 ± 0.09^{aA}	10.52 ± 0.09^{aA}	10.52 ± 0.15^{aA}	10.53 ± 0.08^{aA}	10.51 ± 0.13^{aA}	10.53 ± 0.23^{aA}	10.52 ± 0.23^{aA}
Group-B(Lead@10mg/kg)	10.47 ± 0.23^{aA}	10.40 ± 0.12^{aA}	10.47 ± 0.12^{aA}	10.42 ± 0.22^{aA}	10.16 ± 0.17^{bB}	9.87 ± 0.32^{bC}	10.19 ± 0.17^{bB}	10.24 ± 0.13^{cB}
Group-C (λ-cyhalothrin @2.25mg/kg)	10.44 ± 0.41^{aA}	10.38 ± 0.11^{aA}	10.50 ± 0.32^{aA}	10.43 ± 0.15^{aA}	10.11 ± 0.11^{bB}	9.73 ± 0.24^{cC}	10.22 ± 0.25^{bAB}	10.37 ± 0.24^{bA}
Group-D(Lead@10mg/kg +λ-cyhalothrin @2.25mg/kg)	10.51 ± 0.13^{aA}	10.44 ± 0.24^{aA}	10.46 ± 0.25^{aA}	10.47 ± 0.32^{aA}	9.85 ± 0.31^{cB}	9.23 ± 0.14^{dC}	10.11 ± 0.27^{bAB}	10.19 ± 0.17^{dAB}

Values are in Mean ± SE, Similar superscript do not differ significantly at 5% (P<0.05) Capital superscripts represent significance within the groupSmall letter superscripts represent significance between the group

Table 3: Showing the effect of Lead, λ-cyhalothrin, Lead + λ-cyhalothrin on Packed cell volume (%) in goats. (n=4).

Treated Group(s)	Treatment Period						Post Treatment Period	
	Zero day	3rd day	7th day	14th day	21st day	28th day	7th day	14th day
Group A(Control)	34.54±0.03^{aA}	34.55±0.09^{aA}	34.56±0.06^{aA}	34.58±0.06^{aA}	34.60±0.06^{aA}	34.62±0.05^{aA}	34.58±0.06^{aA}	34.63±0.03^{aA}
Group B (Lead@10mg/kg)	34.60±0.07^{aA}	34.57±0.08^{aA}	34.05±0.06^{bB}	33.89±0.02^{bB}	33.55±0.03^{bC}	33.32±0.04^{bD}	33.70±0.03^{bBC}	33.76±0.03^{bB}
Group C (λ-cyhalothrin @2.25mg/kg)	33.59±0.02^{aA}	33.51±0.08^{bA}	33.13±0.02^{cB}	32.82±0.02^{cC}	32.54±0.03^{cD}	32.28±0.04^{cE}	32.49±0.04^{cDE}	33.05±0.04^{cB}
Group D (Lead@10mg/kg + λ-cyhalothrin @2.25mg/kg)	34.43±0.03^{aA}	33.39±0.09^{bA}	33.25±0.06^{cB}	32.80±0.02^{cC}	32.33±0.03^{cD}	32.01±0.04^{cE}	32.24±0.02^{cB}	32.34±0.03^{cA}

Values are in Mean±SE, Similar superscript do not differ significantly at 5% (P<0.05) Capital superscripts represent significance within the group Small letter superscripts represent significance between the groups

Table 4: Showing the effect of Lead, λ-cyhalothrin, Lead + λ-cyhalothrin on Total erythrocyte count (million/µl) in goats (n=4).

Treated Group(s)	Treatment Period						Post Treatment Period	
	Zero day	3rd day	7th day	14th day	21st day	28th day	7th day	14th day
Group-A (Control)	10.41±0.15^{aA}	10.39±0.27^{aA}	10.43±0.04^{aA}	10.34±0.05^{aA}	10.35±0.03^{aA}	10.47±0.02^{aA}	10.65±0.05^{aA}	10.74±0.04^{aA}
Group-B (Lead@10mg/kg)	10.34±0.13^{aA}	10.17±0.33^{bA}	10.01±0.04^{bB}	9.84±0.03^{bC}	9.60±0.02^{bC}	9.45±0.04^{bD}	9.68±0.03^{bC}	9.84±0.03^{bC}
Group-C (λ-cyhalothrin @2.25mg/kg)	10.55±0.24^{aA}	10.01±0.53^{cA}	9.88±0.04^{bB}	9.54±0.04^{cC}	9.33±0.04^{cD}	9.15±0.03^{cE}	9.21±0.02^{cE}	9.36±0.04^{cD}
Group-D (Lead@10mg/kg + λ-cyhalothrin @2.25mg/kg)	10.47±0.32^{aA}	10.19±0.43^{bA}	9.98±0.02^{bB}	9.55±0.02^{cC}	9.33±0.02^{cD}	9.01±0.03^{dG}	9.21±0.02^{cF}	9.30±0.04^{cE}

Values are in Mean±SE, Similar superscript do not differ significantly at 5% (P<0.05) Capital superscripts represent significance within the group Small letter superscripts represent significance between the groups

Total leucocytes count

After repeated exposure of λ-cyhalothrin on Group-C goats, result in a significant decrease in the WBCs count as compared to control goats (Group-A) (Table 5). Similar observations has also been reported by Ahrar *et al*. (2010) [2] and Dahama *et al*. (2009) in rabbits and rats exposed to λ-cyhalothrin for 14 days and 4 weeks period, respectively. Decreased leukocyte count in λ-cyhalothrin treated groups could be due to its direct cytotoxic effects (Benjamin, 1978) [5]. Other likely-hood of leukopenia could be the fact that, benzene ring of the pyrethroids acts as hapten and when merges with protein ingredients of the leukocytes, the new leucocyte behaves as an antigen against which antibodies are developed. The formed antibodies react to leukocytes and cause either lysis or agglutination, (Benjamin, 1978) [5] which eventually leads to devastation of leukocyte resulting in decreased leukocyte counts.

Whereas, repeated exposure of lead-acetate on Group-B goats a significant increase in WBC count was found as compared to control goats (Group-A). Similar finding has also been reported in lead acetate treated buffalo calves (Brar *et al*., 1995) [7]. Also a threefold increase in neutrophil and monocyte count and severe leukocytosis has been reported in the young rats exposed to lead (Hogan and Adams, 1979) [15]. Increase in leukocyte counts in lead acetate treated groups could be due to the lead-induced inflammation or whenever any toxicity/intoxication occurs in body, the body immune system enhances the production of WBC (Yagminas *et al*., 1990) [39].

An interesting finding in the present study is that when goats were exposed to combination of lead-acetate and λ-cyhalothrin (group-D) induces a non-significant increase in total leucocytes count as compared to lead acetate exposed goats (Group-B). This can be attributed to the counter-balancing act of λ-cyhalothrin producing leucopenia and lead induced inflammatory increase of leucocytes, revealing a non-significant increase in goats co-exposed to lead acetate and λ-cyhalothrin. A similar finding has also been seen in wistar rats repeatedly co-exposed to cypermethrin and lead for 28 days (Institoris *et al*., 2001) [17].

Table 5: Showing the effect of Lead, λ-cyhalothrin, Lead + λ-cyhalothrin on Total leucocytes count (thousands/µl) in goats (n=4).

Treated Group(s)	Treatment Period						Post Treatment Period	
	Zero day	3rd day	7th day	14th day	21st day	28th day	7th day	14th day
Group-A (Control)	9.69±0.02^{aA}	9.70±0.04^{aA}	9.69±0.05^{bA}	9.71±0.06^{cA}	9.76±0.03^{cA}	9.74±0.03^{cA}	9.73±0.03^{cA}	9.70±0.06^{cA}
Group-B (Lead@10mg/kg)	9.60±0.03^{aD}	9.62±0.02^{aD}	9.71±0.03^{bD}	9.94±0.02^{bC}	10.14±0.03^{bB}	10.32±0.01^{bA}	10.33±0.02^{bA}	10.29±0.02^{bA}
Group-C (λ-cyhalothrin @2.25mg/kg)	9.58±0.01^{aA}	9.61±0.01^{aA}	9.65±0.02^{bA}	9.49±0.01^{dB}	9.37±0.02^{dC}	9.17±0.02^{dD}	9.20±0.01^{dD}	9.21±0.01^{dD}
Group-D (Lead@10mg/kg +λ-cyhalothrin @2.25mg/kg)	9.53±0.04^{aD}	9.65±0.02^{aD}	9.84±0.03^{aD}	10.15±0.03^{aC}	10.51±0.03^{aB}	10.72±0.03^{aA}	10.73±0.04^{aA}	10.68±0.05^{aA}

Values are in Mean±SE, Similar superscript do not differ significantly at 5% (P<0.05) Capital superscripts represent significance within the group Small letter superscripts represent significance between the groups

Osmotic fragility of erythrocytes

A significant decrease in erythrocyte osmotic fragility was found in lead-acetate exposed goats (Group-B) as compared to control goats (Group-A) (Table 6, 7 & 8). Similar finding has also been observed on lead-acetate treated rats for 3 months (Levander *et al*., 1977) [22]. The decrease in osmotic fragility of erythrocytes in lead treated goats thought to be because of tanning of cell membrane by lead, thereby toughening it and rendering the erythrocyte less susceptible to osmotic stress (Passow *et al*., 1961) [31].

However, a significant increase in osmotic fragility of erythrocytes was found in λ-cyhalothrin exposed goats (Group-C) as compared with control goats (Group-A). A similar increase in fragility was reported in cypermethrin

exposed rats for 14 days (Salwa and Hala, 2004) [36]. The increase in osmotic fragility by pyrethroids can be explained by release of haemoglobin in allethrin treated human erythrocytes (Gabbianelli *et al*., 2002) [12]. In another study, aggregation of cypermethrin occurs in the lipid bi-layer of the membrane resulting in increase of membrane instability (Moya-Quiles *et al*., 1995) [27]. Thus pyrethroid-insecticides induce change(s) in the erythrocytes membrane which may consequently increase the osmotic fragility (Moya-Quiles *et al*., 1995) [27].

A significant increase in osmotic fragility was found in Group-D goats (lead-acetate+ λ-cyhalothrin) as compared to Group-B (lead-acetate) and Group-A control goats, whereas a non-significant change (increase) has been noted as compared to group-C goats (λ-cyhalothrin). Tanning of RBC-membrane by lead leads to membrane toughening, rendering it resistant to mechanical trauma (Passow *et al*., 1961) [31] and tough erythrocyte membrane may interfere in incorporation of pyrethroids into the lipid-layer of erythrocytes which may be one of the reason the degree of expected increase in osmotic fragility has not been seen in combined effect (Group-D) as compared to group-C.

Table 6: Showing the effect of osmotic fragility (%) on erythrocytes of zero day obtained from Lead, λ-cyhalothrin, Lead + λ-cyhalothrin-treated-goats (n=4).

Treated Group(s)	Effect of different NaCl concentrations on erythrocytes of day 0 of treatment period					
	0.9	0.7	0.5	0.3	0.1	0
Group-A (Control)	0.00±0	0.58±0.024^{a}	16.28±0.316^{a}	70.44±0.262^{a}	81.63±0.186^{a}	100±0
Group-B (Lead@10mg/kg)	0.00±0	0.56±0.019^{a}	16.49±0.257^{a}	69.64±0.202^{a}	80.03±0.189^{a}	100±0
Group-C (λ-cyhalothrin @2.25mg/kg)	0.00±0	0.59±0.033^{a}	17.04±0.901^{a}	71.11±0.171^{a}	81.14±0.454^{a}	100±0
Group-D (Lead@10mg/kg + λ-cyhalothrin @2.25mg/kg)	0.00±0	0.53±0.018^{a}	16.71±0.470^{a}	70.74±0.472^{a}	80.31±0.624^{a}	100±0

Values are in Mean±SE, Similar superscript do not differ significantly at 5% (P<0.05) Small letter superscripts represent significance between the groups

Table 7: Showing the effect of osmotic fragility (%) on erythrocytes of 28 days obtained from Lead, λ-cyhalothrin, Lead + λ-cyhalothrin-treated-goats (n=4).

Treated Group(s)	Effect of different NaCl concentrations on erythrocytes after treatment period of 28 days					
	0.9	0.7	0.5	0.3	0.1	0
Group-A (Control)	0.00±0	0.58±0.024^{b}	16.28±0.316^{b}	70.44±0.262^{b}	81.63±0.186^{b}	100±0
Group-B (Lead@10mg/kg)	0.00±0	0.44±0.020^{c}	15.44±0.225^{c}	65.96±0.351^{c}	76.76±0.284^{c}	100±0
Group-C (λ-cyhalothrin @2.25mg/kg)	0.00±0	0.87±0.018^{a}	44.25±0.881^{a}	75.52±0.722^{a}	88.35±0.443^{a}	100±0
Group-D (Lead@10mg/kg + λ-cyhalothrin @2.25mg/kg)	0.00±0	0.90±0.044^{a}	45.09±0.243^{a}	75.77±0.258^{a}	88.53±0.343^{a}	100±0

Values are in Mean±SE, Similar superscript do not differ significantly at 5% (P<0.05) Small letter superscripts represent significance between the groups

Table 8: Showing the effect of osmotic fragility (%) on erythrocytes of post-treatment period of 14 days obtained from Lead, λ-cyhalothrin, Lead + λ-cyhalothrin-treated-goats (n=4).

Treated Group(s)	Effect of different NaCl concentrations on erythrocytes after Post-treatment period of 1 days					
	0.9	0.7	0.5	0.3	0.1	0
Group-A(Control)	0.00±0	0.58±0.024^{c}	16.28±0.316^{c}	70.44±0.262^{c}	81.63±0.186^{c}	100±0
Group-B(Lead@10mg/kg)	0.00±0	0.49±0.014^{d}	15.40±0.047^{d}	68.49±0.075^{d}	78.15±0.200^{d}	100±0
Group-C (λ-cyhalothrin @2.25mg/kg)	0.00±0	0.74±0.026^{a}	26.05±0.505^{a}	73.30±0.321^{a}	86.14±0.156^{a}	100±0
Group-D (Lead@10mg/kg+ λ-cyhalothrin @2.25mg/kg)	0.00±0	0.62±0.017^{b}	21.36±0.314^{b}	70.98±0.280^{b}	82.97±0.130^{b}	100±0

Values are in Mean±SE, Similar superscript do not differ significantly at 5% (P<0.05) Small letter superscripts represent significance between the groups

Conclusion

The present study suggested that Lead acetate and λ-cyhalothrin treated-goats alone produced hematological changes within the same group of goats and also when compared to control goats. Such changes were more prominent and consistent with co-administration of two toxicants.

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