

HEPATIC AND NEURAL TOXICITY AND TISSUE RESIDUE OF CYPERMETHRIN IN MALE SOMALI SHEEP (*BERBERA BLACKHEAD*)

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ABSTRACT

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The effect of type II synthetic pyrethroid, cypermethrin on selected physiological and biochemical parameters of liver and neural system were studied in male Somali sheep. In addition, the residue of cypermethrin in different tissues and body excreta were also evaluated. Two tested doses (6 and 12 mg /kg b.wt/day) of cypermethrin were given orally to sheep for 63 consecutive days. A vehicle-control group of sheep given corn oil (0.1 ml/kg/day) only was used for comparison. Investigated animals of all groups were slaughtered 24 h after the last dose. No fatality was recorded during the course of this study. Cypermethrin produced significant increase in the weights of liver and spleen, while there were no effects on the weights of brain, kidneys, heart and testes. A significant increase in liver aspartate amino transaminase (AST) and alanine amino transaminase (ALT) activities and a significant decrease in liver lactate dehydrogenase (LDH) activity were recorded in the pesticide-treated animals. Significant decreases were observed in brain Na⁺, K⁺-ATPase and Mg⁺⁺-ATPase in cypermethrin-treated animals that were dose-dependant. Residue analysis revealed higher levels of cypermethrin in spleen, kidneys and muscle than liver. Residues of tested pesticide were detected in all samples of urine and faeces of treated sheep, and were dose-dependent. From this study it can be concluded that exposure of farm animals for long periods to cypermethrin pesticide will affect their physiological and biochemical parameters with subsequent adverse effect on animal health and production. Moreover, the presence of large amount of tissue residues of this compound in animal tissues and excreta could affect human health as well. Therefore, farm animals should not be exposed to these pesticides for long times via food or water.

Key words: *Cypermethrin, hepatic toxicity, neural toxicity, tissue residues, Somali sheep*

INTRODUCTION

Pesticides constitute the major source of potential environmental hazards not only for animals but also to human when they become part of food chains (Abd-Alla *et al.*, 2002). Various chemicals have been used as pesticides in public health programs, veterinary and agriculture. Greater reliance on the use of pesticides to maintain higher agricultural productivity appears inevitable as the demand for food increases with increasing population (Abou Zeid *et al.*, 1993). Intensive agriculture activities require the application of large quantities of pesticides annually. The long term application of these pesticides is always expected to induce pesticide residues accumulation in soil, water, and in

the general environment, thereby posing a serious threat to public health (El-Sebae, 1990; Abdul Mujeeb and Shakoori, 2007). It is believed that numerous undocumented cases of acute poisoning to human, farm animals, honey bees, and fish, due to direct dermal contact or ingestion of contaminated food and water occur annually (Abdul Mujeeb and Shakoori, 2007).

Synthetic pyrethroid is one of the main classes of insecticides widely used in agriculture. Pyrethroids are preferred above organophosphates, carbamates and organochlorines as these have high efficiency, low toxicity and easy biodegradability (Sharaf *et al.*, 2010). For more than 30 years, pyrethroids are in use for home formulations and agricultural purposes and

these insecticides cover nearly one-fourth of the worldwide market (Ahmad *et al.*, 2012). In spite of claims of low mammalian toxicity of pyrethroid, evidence is gradually accumulated against it as several reports described and documented the toxicological effects of various pyrethroid insecticides in many species of animals (Shakoori *et al.*, 1988; Moore and Waring, 2001; Abdul Mujeeb and Shakoori, 2007; Khan *et al.*, 2012). Cypermethrin (CY) (type II synthetic pyrethroid) lipophilic in nature, is considered to be less toxic due to its speedy insect killing properties and having low toxicity to mammalian tissues (Aslam *et al.*, 2010). However, it is fairly toxic when applied dermally or administered orally (Luty *et al.*, 1998 and Aslam *et al.*, 2010). Moreover, it can exert significant adverse effects in non-target species including humans and livestock animals (Baselt, 2008).

The magnitude of toxic effects of pesticides depends mainly on the type and dose of compound, duration of exposure, species and age of animals and other environmental factors (Dunnick *et al.*, 1984). Farm animals have been contaminated in a variety of ways, thus possibly affecting the animal's growth and production. Sheep are usually dipped or treated with insecticides each year in order to prevent and control ectoparasites. Cypermethrin is being increasingly used as the active ingredient in many dips which are used to prevent and treat ticks, lice and scab on sheep (Hardeng *et al.*, 1992 and Khan *et al.*, 2012). Therefore, the current study aimed to investigate the effect of long term exposure to cypermethrin, one of the synthetic pyrethroids, on some hepatic and neural parameters and to determine its tissue residues in male sheep after repeated oral administration.

MATERIALS and METHODS

Pesticide

An active type II synthetic pyrethroid insecticide (cypermethrin) was used in the present study. Cypermethrin [25% E.C (RS)-alpha-cyano-3-phenoxybenzyl (IRS)-cis-, trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylate] (Mitchell Cotts Chemicals, Belgium). Cypermethrin was prepared in corn oil and were administered orally in gelatin capsules to sheep.

Animals and treatment

Eighteen male Somali sheep (*Berbera Blackhead*) aged eight to ten months of 27.5 ± 2.36 kg average body weight were used in this study. The animals were housed in shelter and fed on roughage (rice straw) and concentrate supplement according to their actual requirements (NRC, 1985). The concentrate contained at least 61% total digestible nutrients (TDN) and 11.5 % digestible proteins (DP). Feed and water were provided to animals *ad libitum*

throughout the experiment. The animals were divided into 3 groups of six animals each. The first group was treated orally with corn oil daily at 0.1 ml/kg for 63 days and kept as vehicle control. The second and third groups were orally treated with cypermethrin at low and high doses of 6 and 12 mg/kg body weight/day, respectively (Yousef *et al.*, 1998) for 63 successive days. Doses of tested pesticide were formulated weekly to meet the weight changes. The dose for each animal was contained in a gelatin capsule that was inserted orally into the esopharyngeal region with the help of a glass rod. Animals were observed daily for the nature and onset of toxic signs. Body weights were recorded at the beginning of the experiment and every week thereafter. One day after the last treatment, all investigated animals were slaughtered and their liver, kidney, heart, spleen, testis, brain and lung were immediately excised and washed in cold saline. The organs were weighed after blotting them dry and the organ: body weight ratio was calculated.

Biochemical studies

Freshly removed liver and brain were washed using chilled saline solution and homogenized (10% w/v) in 0.25 M ice cold sucrose solution in a Potter-Elvehjem type homogenizer. The homogenates were centrifuged at 700 xg for 10 min. at 4 °C to remove cell debris. The liver supernatant was used for estimation of aspartate amino transaminase (AST) and alanine amino transaminase (ALT), acid phosphatase (AcP), alkaline phosphatase (AIP) and lactate dehydrogenase (LDH) activities according to Reitman and Frankel (1957); Bergmeyer (1963); Bessey *et al.* (1964) and Cabaud and Wroblewski (1958), respectively, using commercially available kits (Pasteur Lab, USA). The brain supernatant was used for estimation of acetylcholinesterase (AChE) activity according to Ellman *et al.* (1961). Brain tissues of sheep were prepared as described by Koch (1969) for determination of Na^+ , K^+ -ATPase and Mg^{++} -ATPase activities. ATPase activities were assayed according to Cutkomp *et al.* (1971) where inorganic phosphate was determined according to the method of Fiske and Subbarow (1925). Protein in brain ATPase preparations was estimated by the method of Lowry *et al.* (1951).

Residue analysis

Samples of urine (100 ml) and faeces (100 gm) were collected once a week and continued throughout the experimental period. Kidney (50 gm), spleen (25 gm), liver (50 gm) and forequarter muscles (100 gm) were collected from the sacrificed animals (control and treated). Levels of cypermethrin in all samples were analysed according to Braun and Stanek (1982), and AOAC (1984), respectively. Gas chromatograph (GC) (Hewlett Packard series 5890) was used. GC equipped with ^3H -electron capture detector (ECD) to

detect cypermethrin. Megabore column HP-608 part No. 190955-023; (30 m x 0.53 mm i.d x 0.5 µm film thickness) was used. Split injection (0.8 min. hold) was applied with temperature at 220 °C, helium as carrier gas at 6 ml/min. flow rate. ECD and NPD temperatures were at 270 °C and 225 °C, respectively. Column temperatures for cypermethrin resolution was at 170 °C. According to these conditions, cypermethrin which contains a third asymmetric center, was resolved into an envelope of three peaks with retention times of 21.93, 22.66 and 23.34 min.

For the assessment of the extraction efficiency of cypermethrin, triplicate fortified samples with 100 ng of technical tested pesticides were made directly to urine and the extract of each of faeces, kidneys, spleen, liver and muscles samples of control animals. Reported levels of cypermethrin in the collected

samples from control and treated animals had not been adjusted on the basis of percent recoveries. This was due to the very high percent of recovery.

Statistical significance between experimental and control values were calculated according to Student's "t" test as described by Fisher (1950) using SPSS 16.0.

RESULTS

Organ: body weight ratio

Sheep in all groups survived to the end of the study. A significant increase in relative liver and spleen weights was observed in sheep treated with cypermethrin, and a dose-response relationship was observed (table 1). Weights of brain, heart kidneys and testis were not affected (data not shown).

Table 1: Mean body weight and relative organ weights of slaughtered male sheep after oral daily administration of Cypermethrin.

Pesticide	Dose (mg/kg/day)	Body weight (kg)	Relative weight (g/g) × 10 ³	
			Liver	Spleen
			Corn oil (control)	0.1 (ml/kg/day)
Cypermethrin	6 (mg/kg/day)	29.20±3.86	17.09±1.58*	6.98±2.11*
	12 (mg/kg/day)	30.40±2.89	17.54±1.51*	8.99±2.55*

Values represent the mean ± SE of three animals.

* Within columns, significantly different from control (P < 0.05).

Liver and brain biochemistry

The activities of liver AST, ALT, AIP, AcP, and LDH are shown in table (2). Liver AST and ALT activities in male sheep were significantly increased after treatment with cypermethrin (6, 12 mg/kg body weight, respectively).

Table 2: Enzymatic status of liver in male sheep after oral administration of Cypermethrin.

Parameters ^(a)	Control	Cypermethrin	
		Doses (mg/kg/day)	
		6	12
AST (U/L)	14.71 ±1.53	21.2 ±1.88*	25.9 ±3.14*
ALT (U/L)	3.02 ±0.25	3.66 ±0.27*	4.24 ±0.43*
AIP (U/L)	0.43 ±0.02	0.44 ±0.03	0.45 ±0.04
AcP (U/L)	1.96 ±0.08	1.94 ±0.06	1.98 ±0.07
LDH (U/L)	23.12 ±2.06	16.3 ±1.14*	14.2 ±1.21*

Values represent the mean ± SE of three animals.

(a) IU/g = International unit, the amount of the enzyme that under defined assay conditions will catalyze 1 mole of substrate per minute per gram liver tissue.

* Within rows significantly different from control (P<0.05).

Table 3 shows the effect of oral administration of cypermethrin on the activities of brain enzymes. Cypermethrin at both doses did not show any significant change in AChE activity. Cypermethrin treated animals at both doses show a significant decrease in Na⁺, K⁺-ATPase and Mg⁺⁺-ATPase activities as compared to control.

Table 3: Brain biochemical changes in male sheep after administration of Cypermethrin.

Parameters ^(a)	Control	Cypermethrin	
		Doses (mg/kg/day)	
		6	12
AChE ^a	31.67 ±1.23	30.58 ±1.12	31.13 ±1.08
Na ⁺ , K ⁺ -ATPase ^b	66.21 ±3.20	47.51 ±2.83*	41.8 ±2.24*
Mg ⁺⁺ -ATPase ^b	36.10 ±2.14	22.71 ±1.78*	19.3 ±1.45*

Values represent the mean ± SE of three animals.

^(a) Activity expressed in μmoles substrate hydrolysed/min./g tissue.

^b Activity expressed in μmole Pi/g protein/min.

* Within rows significantly different from control (P < 0.05).

Residue analysis

Residues of cypermethrin were below the detection levels (50 pg/μl) in all samples collected from control animals. Average recoveries of 100 ng of cypermethrin from urine, feces, kidneys, spleen, liver and forequarter muscles of control sheep were ranged from 64 to 96%, and the relative standard error for detected levels ranged between 2.34 and 5.49% (Table 4).

Table 4: Percent recovery of 100 ng of cypermethrin in feces, urine, kidney, spleen, liver and muscle of control sheep (mean ± SE).

	Feces	Urine	Kidney	Spleen	Liver	Muscle
Recovery %	79.54 ±2.37	96.37 ±2.85	90.2 ±2.34	87.0 ±2.66	89.6 ±2.68	74.1 ±3.89

The results of cypermethrin residues in urine and feces during the experimental period are shown in table 5. These results indicated that the residues of cypermethrin were detected in all urine and feces samples of treated animals.

Table 5: Residue levels in feces (ng/g) and urine (ng/ml) during treatment of male sheep with pesticides (mean ± SE of three animals).

Doses	Cypermethrin Treatment (weeks)								
	1	2	3	4	5	6	7	8	9
	Feces								
6 mg/kg/day	11.31 ±1.64	15.92 ±0.45	16.0 ±1.71	14.43 ±1.78	31.79 ±1.49	53.49 ±2.90	52.31 ±1.39	54.62 ±5.30	50.37 ±3.34
12 mg/kg/day	14.59 ±0.67	17.65 ±2.19	28.09 ±0.89	23.67 ±2.76	51.09 ±4.34	64.73 ±4.60	66.03 ±4.54	63.51 ±4.34	69.35 ±2.47
	Urine								
6 mg/kg/day	18.64 ±1.81	32.91 ±1.44	41.63 ±1.88	36.41 ±2.83	35.68 ±3.03	37.19 ±1.65	45.75 ±3.43	56.19 ±3.85	72.04 ±3.66
12 mg/kg/day	23.69 ±0.36	48.89 ±3.25	47.1 ±2.89	57.06 ±3.00	52.83 ±4.60	60.16 ±3.00	72.97 ±5.09	116.0 ±8.16	102.3 ±6.89

Results on the residues of cypermethrin in the tissues of kidneys, spleen, liver and forequarter muscles of treated animals after 63 days are presented in table 6. The results indicated that cypermethrin was detected in all tissue samples of treated animals. The pesticide residues in tissues of control animals were under detection limits (50 pg/ μ l).

Table 6: Residual levels (ng/g) of cypermethrin in tissues of male sheep after treatment (mean \pm SE of three animals).

Tissues	Cypermethrin Doses	
	6	12
Kidney	64.2 \pm 3.05	156.1 \pm 3.97
Spleen	69.0 \pm 4.04	148.5 \pm 2.98
Liver	12.2 \pm 0.20	14.3 \pm 0.33
Muscle	62.4 \pm 3.03	84.6 \pm 4.25

DISCUSSION

Cypermethrin, (type II synthetic pyrethroid), is being increasingly used as dips for treatment and control of ticks, lice and scab on sheep (Khan *et al.*, 2012). The speedy insect killing properties of cypermethrin is believed to reduce its toxicity to mammalian tissues. However, it is fairly toxic when applied dermally or administered orally (Baselt, 2008; Aslam *et al.*, 2010).

The results of the current study revealed significant dose-dependant increase in relative liver and spleen weights in sheep treated with cypermethrin. The significant liver enlargement after cypermethrin exposure indicated an increase in the functional load of the organ. These findings are in agreement with the results reported by Hend and Butterworth (1977) and US-EPA (1984) in rats treated with cypermethrin. An increase in spleen weight was observed in the present study for sheep being treated with cypermethrin.

With regard to hepatic toxicity, current results showed significant increase of hepatic AST and ALT activities in male sheep after treatment with cypermethrin. The elevation AST and ALT activities was dose dependent. On the other hand, hepatic tissue activity of LDH was significantly lower than those of the control in sheep treated with cypermethrin. Transaminases (AST and ALT) are important and critical enzymes in the biological processes. These enzymes are involved in the breakdown of amino acids into α keto acid which are routed for complete metabolism through the Krebs' cycle and electron transport chain. Consequently, they are considered as a specific indicator for liver damage (Harper *et al.*, 1979). An increased AST activity was observed by Shakoori *et al.* (1988) in albino rats administrated cypermethrin. Shakoori *et al.* (1992) reported increased liver transaminases

(AST and ALT) activities after cyhalothrin administration in rabbits. The dosages of cypermethrin given for 63 days did not elicit significant changes in the liver phosphatases, as it is well known that phosphatases are responsible for transport mechanisms involving phosphates. The hepatic LDH activity indicates the switching over of anaerobic glycolysis to aerobic respiration. The decreased hepatic LDH activity may be due to the hepatocellular necrosis leading to leakage of the enzyme and/or enzyme inhibition. The results of this study showed a significant decrease in LDH activity of cypermethrin and dimethoate treated sheep. These results are in agreement with the results reported by Wang and Zhai (1988).

With regard to neural toxicity, brain did not show significant changes in the activity of acetylcholinesterase (AChE) in sheep treated with both doses cypermethrin compared with control. Brain ATPase is a key enzyme in cellular water balance and in osmoregulation in the whole animal. Cypermethrin treated animals at both doses show a significant decreases in brain Na⁺, K⁺-ATPase and Mg⁺⁺-ATPase activities. Several classes of pesticides were known to inhibit ATPases activities (Koch, 1969; Cutkomp *et al.*, 1976). Several opinions were expressed for such an inhibition in the ATPase activity in the cellular system. Inhibition indicates an overall disruption in the energy metabolism. Na⁺, K⁺-ATPase enzyme is associated with lipoprotein in the form of a complex (Nakao *et al.*, 1974). If a lipophilic compound were to come in contact with this lipoprotein and partitioning into the lipid fraction occurred, an allosteric change could occur which could alter the activity of the enzyme. Kinter *et al.* (1972) hypothesized that lipophilic pesticides exert their biologic effects on ATPase system by interacting with the phospholipid-activating component of the enzyme complex. The lipophilic partitioning of ATPase enzyme by

cypermethrin may produce allosteric change resulting in decreased ATPase activity. A decrease in Mg^{++} -ATPase and Na^+ , K^+ -ATPase activities in the rat was reported by La Rocca and Carlson (1979).

Residues of pesticides were below the detection levels (50 pg/ μ l of cypermethrin) in all samples collected from control animals. Average recoveries of 100 ng of cypermethrin from urine, feces, kidneys, spleen, liver and forequarter muscles of control sheep were ranged from 64 to 96%, and the relative standard error for detected levels of pesticides ranged between 2.34 and 5.49% (table 4).

The present study showed that residues of cypermethrin were detected in all urine and feces samples of treated animals. This indicated that the main routes for cypermethrin excretion from the body were through both urine and feces. Croucher *et al.* (1985) found that the major routes for elimination of oral administration of cypermethrin in cows were via both urine (approximately 50 %) and feces (approximately 40%). The elimination pattern in sheep, given one oral dose of cypermethrin (3.9 mg/kg body weight), showed that 41% of the administered dose excreted in the urine and 20 % was eliminated in feces (Crawford and Hutson, 1977). The detected levels of pesticides were dose-dependent. On the other hand, the results of cypermethrin residues in the tissues of treated animals revealed the detection of cypermethrin in all tissue samples of treated animals. Moreover, the present results showed that the residue levels of cypermethrin were in the following decreasing order: kidneys > spleen > muscles > liver at levels ranging from 12.2 to 156.1 ng/g for cypermethrin. Croucher *et al.* (1985) found that the residues of cypermethrin were detected in milk, blood, liver, kidneys and subcutaneous and renal fat of cows. Crawford and Hutson (1977) also reported that the residues of cypermethrin were detected in muscle, liver, kidneys and renal fat of sheep. Cattle sprayed once with 0.1% and 0.2% of cypermethrin showed that the residues in muscle, liver, and kidneys were \leq 0.005 mg/kg in tissues and < 0.01 mg/kg in fat. In cattle treated twice with cypermethrin, fat samples contained residues ranging from 0.01 to 0.05 mg/kg tissue (Bosio, 1979).

In conclusion, the obtained results indicate that cypermethrin produces moderate toxic effects in different animal systems including hepatic and neural functions. Concerning the record of cypermethrin residues in feces and urine as well as other body tissues and organs, great attention should be taken during its field application to avoid the possible significant adverse effects in non-target species including humans and other livestock animals.

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دراسة تأثير سمية مركب السيبرميثرين على الكبد والأعصاب ومنتجاتها في الانسجة في ذكور الأغنام الصومالية
(بربرا بلاكهد)

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تم اجراء هذه الدراسة لمعرفة تأثير مركب البيريثرويد المصنع نوع ٢ (سيبرميثرين) على بعض الخواص الفسيولوجية والبيوكيميائية للكبد والجهاز العصبي في ذكور الأغنام الصومالية. كما تم ايضا تقدير مستويات مركب السايبرميثرين في انسجة ومخرجات الحيوانات محل الدراسة. تم اعطاء مركب السيبرميثرين عن طريق الفم إلى الأغنام لمدة ٦٣ يوم متتالية وذلك باستخدام جرعتين (٦ و ١٢ مج / كغ / يوم). للمقارنة تم استخدام مجموعة طابطة من الأغنام أعطيت زيت الذرة (٠.١ مل / كغ / يوم). وطوال فترة التجربة لم يتم تسجيل اي حالات وفاه وقد ذبح جميع الحيوانات ٢٤ بعد ساعة بعد آخر جرعة. هذا وقد اظهرت نتائج الدراسة ان مركب السيبرميثرين تسبب في حدوث زيادة كبيرة في أوزان الكبد والطحال في حين انه لم يكن هناك أي تأثير على أوزان المخ والكلية والقلب والخصيتين. بالنسبة لتأثير مركب السيبرميثرين على الكبد اظهرت الدراسة حدوث زيادة معنوية في نشاط أنزيمي أسبرتيت أمينو ترانس أمينيز والأنين أمينو ترانس أمينيز وانخفاض معنوي في نشاط إنزيم اللاكتيك دي هيدروجينيز في كبد الحيوانات المعالجة بالمبيد بالمقارنة بالمجموعة الطابطة. اما فيما يخص الجهاز العصبي فكان هناك انخفاض معنوي في نشاط إنزيمات الصوديوم والپوتاسيوم ادنيوزين ثلاثي الفوسفاتيز والماغنسيوم ادنيوزين ثلاثي الفوسفاتيز في مخ الحيوانات المعاملة بالسيبرميثرين وزاد هذا التأثير بزيادة جرعه العلاج. هذا وقد كشف تحليل مستويات مركب السيبرميثرين في انسجة الجسم عن وجود مستويات أعلى في الطحال والكلية والعضلات من الكبد في الحيوانات المعاملة بالسيبرميثرين مقارنة بالمجموعة الطابطة. كما اظهرت الدراسة تواجد مستويات من مركب السايبرميثرين في كل من عينات البول والروث المجمعة من الحيوانات المعالجه وكان اخراج بييريثرويد سيبرميثرين يتزايد مع تزايد الجرعة. وقد خلصت الدراسة الى أن تعرض حيوانات المزرعة للتلوث بمبيدات السيبرميثرين يؤدي إلى حدوث تغيرات واضحة في عديد من المعايير البيوكيماوية للجسم مما ينعكس على إنتاجية الحيوان. كما ان وجود مستويات لهذه المبيد في الأنسجة قد ينعكس سلبي على صحة كل من الحيوان والانسان. وعليه يجب تفادي تعرض حيوانات المزرعة للتلوث بالمبيدات عن طريق الغذاء ومياه الشرب.