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ALTERED HEPATIC FUNCTION CONSEQUENT TO IVERMECTIN TREATMENT IN RAMS

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ABSTRACT

This work was carried out on twelve clinically healthy adult Barki rams, divided into two equal groups. The first one was served as control and each animal of the second group was injected subcutaneously with one dose of 0.2 mg ivermectin /Kg body weight. Ivermectin treated group revealed a significant elevation in blood serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, isocitrate dehydrogenase, gamma glutamyl transferase, arginase, sorbitol dehydrogenase and total cholesterol. Meanwhile, ivermectin did not evoke any significant alteration in serum urea and creatinine levels. A very important conclusion that appears to be surfacing from the pervious results is that this study represent further image of the hazardous effects of ivermectin in rams. Ivermectin inflected deleterious effects reflected as hepatic dysfunction.

INTRODUCTION

Ivermectin, a potent broad spectrum antiparasitic drug, is a mixture of two natural fermentation products of *Sterptomyces avermitilis*. Chemically, its constituents are macrocyclic lactone derivatives[1]. The drug immobilizes internal nematodes by blocking the excitatory motor neurons in parasites which contain gamma aminobutyric acid (GABA) in their nervous system [2]. Moreover, the drug had an ovicidal as well as larvicidal effects [3,4]. It's extremely potent antiparasitic activity is greatly precluded by its frequently encountered side effects in horses [5] ; goats [6] and rabbits [7]. The previous side effects could represent a snag in the substantially efficient use of this drug in these species.

Based on the previous issue, the present study was designed to unravel the possible unwanted effects of ivermectin in rams, that could be mirrored as hepatic and /or renal dysfunction.

MATERIAL AND METHODS

Drug:

Ivermectin (Ivomec®) produced by Merk-Sharp and Dohme, USA.

Animals:

Twelve, clinically healthy, adult Barki rams each weighing about 50Kg were used. They were divided into two equal groups. The first one was injected with normal saline and served as control. The second group was subcutaneously injected with one dose of ivermectin ; 0.2 mg/Kg body weight [8].

Blood samples were collected from the jugular vein 1/2 hour (h.) before treatment and 1 h., 4 h., 8 h., 12 h., 24 h., 48 h., 4 days, 7 days, 10 days, 14 days, 21 days, 28 days and 35 days post treatment. The samples were left to clot and centrifuged at 3000 r.p.m. for 20 min.

The separated serum samples were stored at -20°C for biochemical analysis. They were analyzed for levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)[9], total cholesterol (TCH)[10], arginase (ARG)[11], urea (UR)[12], sorbitol dehyrogenase (SDH)[13], isocitrate dehydrogenase (ICD)[14], gamma glutamyl transaminase (GGT)[15] and creatinine (CR)[16].

Statistical analysis:

The results are represented as mean ± S.E. Student's (t) test for paired observations was applied at $P < 0.05$ [17].

RESULTS

Data presented in tables (1) and (2) showed that subcutaneous injection of ivermectin provoked a significant elevation of serum ALT, 24 h. post treatment, that persisted to the end of the experiment.

On the same line, the activity of AST displayed a significant increase, 48 hours post treatment, that was clearly obvious throughout the rest of the experiment. ARG activity disclosed a significant augmentation, 4 hours post treatment, that persisted for 48 h. but declined thereafter to nearly reaching the control level 4days post injection. SDH activity showed a significant elevation, eight hours post drug administration, that was maintained for 4 days post treatment.

Table (3) revealed that ivermectin administration induced a marked augmentation of ALP and GGT activities that were recorded after 12h. and 48h. post treatment respectively and lasted throughout the whole period of the experiment.

Ivermectin treated group exhibited a significant increase of ICD, 4 days post treatment, that was clearly persisted to the 3rd week. On the 28th day post treatment, the previous changes restored its control levels.

Ivermectin treated group exhibited a significant increase of TCH level 4 days post treatment, which lasted for 35 days. On the other hand, ivermectin did not evoke any significant alteration in UR and CR levels as compared with untreated control group (Table 4).

DISCUSSION

It is evident from the present investigation that ivermectin induced a significant elevation of ALT, AST, SDH, ALP, GGT, ICD and TCH levels in Barki rams. Meanwhile, ivermectin did not provoke a significant change in serum urea and creatinine.

Table (1): Effect of ivermectin on the levels of serum ALT and AST (U/L) of rams. (Mean ± S. E) n = 6

Sampling Time	CONTROL GROUP		TREATED GROUP	
	ALT	AST	ALT	AST
0 h.	28.3±2.41	60.2±5.21	30.2±3.34	55.5±6.34
1 h. PT	28.5±2.06	58.8±6.32	30.8±2.25	60.2±6.34
4 h. PT	28.0±2.91	57.1±3.22	32.5±3.52	63.5±6.11
8 h.PT	26.7±2.85	55.2±4.55	33.3±2.01	64.2±4.21
12 h.PT	26.9±3.11	60.1±4.33	35.0±4.51	68.8±6.37
24 h.PT	26.5±3.33	57.2±5.33	40.1±2.59*	73.8±9.54
48 h PT	29.5±2.81	54.3±6.20	45.8±3.33*	79.7±4.88*
4 days PT	30.5±2.56	61.5±3.76	46.3±2.45*	81.5±5.80*
7 days PT	30.7±2.66	59.4±5.79	53.5±2.68*	85.6±6.21*
10 days PT	31.5±2.59	58.3±5.01	56.8±3.47*	87.2±5.87*
14 days PT	28.6±1.59	59.5±3.67	59.5±3.89*	85.6±6.78*
21 days PT	30.5±3.31	61.8±4.08	60.3±4.21*	84.9±6.48*
28 days PT	30.4±3.21	58.6±4.57	55.5±5.21*	78.5±5.87*
35 days PT	32.1±2.34	55.9±6.40	50.3±3.64*	77.5±5.71*

* : Significant from corresponding control value at P< 0.05
0 h. : 30 minutes before treatment. PT: Post treatment

Table (2): Effect of ivermectin on the levels of serum ARG and SDH (U/L) of rams. (Mean ± S. E) n = 6

Sampling Time	CONTROL GROUP		TREATED GROUP	
	ARG	SDH	ARG	SDH
0 h.	10.7±1.33	18.5±2.79	10.0±1.91	17.8±2.97
1 h. PT	10.0±2.01	17.3±1.45	13.2±1.81	16.2±4.81
4 h. PT	11.7±2.57	18.8±2.57	18.5±2.14*	19.8±3.70
8 h.PT	10.8±1.78	16.7±1.61	18.8±2.33*	32.2±2.57*
12 h.PT	10.1±1.54	17.2±2.59	19.8±1.81*	36.8±4.57*
24 h.PT	11.1±1.03	17.5±2.33	20.3±2.86*	34.2±3.33*
48 h.PT	10.9±2.22	18.4±2.87	18.5±2.01*	35.2±4.05*
4 days PT	10.6±1.88	19.3±2.97	13.5±2.55	28.0±2.51*
7 days PT	12.1±2.58	20.2±3.25	14.2±2.22	17.7±2.24
10 days PT	11.8±2.22	21.5±2.67	13.5±2.55	19.4±2.52
14 days PT	10.9±2.34	18.6±3.57	12.3±1.57	23.8±3.27
21 days PT	11.0±0.75	19.1±3.08	11.8±2.33	20.1±2.57
28 days PT	12.3±287	18.7±2.54	12.5±1.89	22.5±3.21
35 days PT	12.4±2.71	16.1±2.71	11.5±2.33	19.7±2.61

* : Significant from corresponding control value at P< 0.05
0 h. : 30 minutes before treatment. PT: Post treatment

Table (3): Effect of ivermectin on the levels of serum ARG and SDH (U/L) of rams. (Mean ± S. E) n = 6

Sampling Time	CONTROL GROUP			TREATED GROUP		
	ALP	GGT	ICD	ALP	GGT	ICD
0 h.	178.5±21.5	35.7±2.54	7.31±1.06	173.4±15.2	33.7±3.21	7.33±0.59
1 h. PT	181.2±19.5	35.2±2.45	7.28±0.85	167.8±18.7	33.4±3.51	7.22±0.81
4 h. PT	162.5±20.1	35.5±2.49	7.49±0.84	197.4±18.1	34.2±3.41	7.42±0.74
8 h.PT	173.4±19.4	33.2±2.97	7.91±0.68	189.4±20.1	33.4±3.45	7.87±0.89
12 h.PT	182.0±16.2	33.7±2.97	8.02±0.81	284.3±24.6*	36.4±3.31	8.88±1.04
24 h PT	181.2±18.2	35.7±2.95	7.81±0.48	305.3±22.2*	39.4±4.12	8.47±0.94
48 h.PT	176.3±18.4	35.2±3.19	7.15±0.85	324.2±25.8*	48.2±2.54*	9.25±1.17
4 days PT	178.2±19.4	34.7±3.25	7.64±0.69	344.2±31.4*	50.1±3.31*	10.92±0.48*
7 days PT	172.6±15.4	35.1±3.71	7.81±0.39	324.2±21.5*	51.4±3.34*	12.80±0.57*
10 days PT	168.7±12.2	35.8±3.57	7.61±0.92	315.8±18.5*	54.2±3.71*	14.52±0.86*
14 days PT	164.8±17.5	34.0±3.31	7.81±0.37	305.0±21.6*	55.2±3.24*	13.82±0.93*
21 days PT	178.5±16.7	36.2±3.49	8.16±0.72	287.7±23.3*	55.1±3.45*	12.89±0.87*
28 days PT	175.4±19.7	35.7±3.54	8.39±0.87	276.9±16.7*	57.1±2.48*	10.17±1.87
35 days PT	181.0±21.0	34.8±2.98	7.81±0.59	257.4±16.2*	48.2±3.50*	9.07±1.40

* : Significant from corresponding control value at P< 0.05
0 h. : 30 minutes before treatment- PT: Post treatment

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Table (4): Effect of ivermectin on the levels of serum TCH (mg/dl) , UR (mmol/L) and CR (µmol/L) of rams (Mean ± S. E) n = 6

Sampling Time	CONTROL GROUP			TREATED GROUP		
	TCH	UR	CR	TCH	UR	CR
0 h.	74.5±4.21	4.81±0.53	86.7±8.66	70.8±7.51	4.67±0.50	85.7±9.71
1 h. PT	77.2±4.24	4.01±0.59	84.5±5.26	75.2±8.91	4.89±0.71	80.3±8.91
4 h. PT	78.5±5.34	4.57±0.64	89.4±7.87	75.4±9.18	5.01±0.87	86.4±5.79
8 h.PT	74.2±6.45	4.33±0.36	81.5±5.57	75.4±5.87	4.69±0.25	86.7±7.89
12 h.PT	75.2±5.47	4.26±0.38	77.9±8.72	84.3±5.01	4.33±0.62	87.9±7.33
24 h.PT	78.4±5.64	4.41±0.78	83.9±8.75	87.2±6.78	4.51±0.35	84.7±9.01
48 h.PT	78.7±5.45	4.21±0.25	88.7±7.67	85.2±9.87	5.02±0.98	86.9±7.24
4 days PT	74.7±4.91	4.64±0.50	83.8±9.24	98.1±5.24*	5.21±0.81	94.6±6.87
7 days PT	72.5±5.78	5.31±0.87	86.7±9.79	105.7±3.87	5.03±0.35	89.8±9.64
10 days PT	77.5±6.34	5.21±0.77	91.8±9.09	108.7±5.51*	5.27±0.48	79.7±7.79
14 days PT	78.9±6.48	4.90±0.67	87.7±6.97	115.4±6.41*	4.81±0.75	75.6±9.48
21 days PT	75.2±8.78	4.71±0.81	77.9±7.98	121.3±7.54*	4.89±0.39	82.9±8.79
28 days PT	78.4±8.71	5.24±0.67	78.9±6.78	122.5±6.54*	5.11±0.72	93.8±10.8
35 days PT	79.4±6.78	5.46±0.49	89.7±8.64	120.5±7.12*	5.49±0.86	91.7±8.75

* : Significant from corresponding control value at P< 0.±05
0 h. : 30 minutes before treatment PT: Post treatment

Unfortunately, our data do not provide us with ready explanation for the previous changes, nevertheless a number of proposals worth discussion could be stated.

Serum alkaline phosphatase activity is of some value in the diagnosis of bile duct obstruction in both cats and dogs, also the level of this enzyme increase in early hepatic damage and is particularly valuable in fatty liver associated with diabetes millitus [18]. The activity also increase when the liver is congested or exposed to toxins [19]. Serum alkaline phosphatase levels are elevated in the cases of acute pancreatitis [20]. Alkaline phosphatase enzyme is excreted in the bile and so its circulating value will increase in the case of liver damage particularly of biliary or interhepatic obstructive types as well as in instance of excessive bone activities [21].

It is proposed that increased serum AST activity is shown following muscular damage, liver damage, myocardial infarction and exposure to various chemicals and drugs [22]. Another possible explanation is cellular destruction in several extrahepatic tissues and thus elevated serum AST activity level is shown to be non specific for hepatic tissue damage [23].

In dogs, cardiac damage of an acute nature result in a marked rise in serum activity of ALT. Similar results are obtained with muscular or liver damage. Most cases of acute pancreatitis exhibit high level of serum ALT activity [18].

Serum level of arginase, a specific enzyme only confined to the liver, will rise rapidly following acute hepatic damage [24].

Hypercholesteremia, is found in nephritic syndrome, nephritis, obstructive jaundice, diabetes mellitus, acidosis, hepatocellular damage, hypothyroidism and pancreatitis [23].

Measurement of serum creatinine levels yields the same diagnostic information concerning renal function as that obtained by the measurement of urea and high serum levels indicate marked impairment of kidney function [25]

Sorbitol dehydrogenase enzyme is an intracellular enzyme. Being located in mitochondria, cytoplasm or both, its circulating levels well be seen in acute extensive cell damage such as severe liver damage or hepatic necrosis [22,26].

Gamma glutamyl transferase is a carbxypeptidase, possibly associated with glutathion metabolism. It is found principally in the kidney but despite this, it is originally used as an indicator of chronic liver damage. It is a membrane bound enzyme, rarely affected by acute hepatic necrosis but elevated in cholestasis [19].

Hepatic necrosis in sheep, calves and horses is also associated with elevation in serum GGT activity [22]. A wealth of information is now available on increased GGT activity associated with myocardial infarction [23].

Isocitrate dehydrogenase activity is elevated in infective hepatitis, malignancy or myocardial infarction and in response to toxic drugs [23].

Given this framework, it is tempting to suggest that the forementioned alterations are imputable, at least in part, to a proposed adverse effect of ivermectin exerted exclusively on hepatic tissues. The previous assumption fits in with the recorded multifocal non suppurative necrosis hepatitis in Nubian goats due to ivermectin treatment [27].

In support of the previous concept, is the fact that the liver generally contains the highest and most

persistent residues of ivermectin[28]. Likewise, ivermectin given subcutaneously into cattle induced a significant increase in serum alkaline phosphatase and ALT levels[29]. Our results are compatible with the previous documented elevations of ALT, AST and alkaline phosphatase, acid phosphatase activities and cholesterol levels in clinically healthy female goats in response to ivermectin subcutaneous injection[6].

Recently, it was reported that rabbits treated with ivermectin, 0.3 mg/kg body weight, demonestrated a significant augmentation of ALT, AST, alkaline phosphatase, acid phosphatase activities and cholesterol levels. Meanwhile, the level of serum urea and creatinine levels did not display any significant alterations[7].

Summing up our observations, it could be concluded that this study tipped the balance toward the hazardous effects of ivermectin therapy in Barki rams that is ultimately mirrored as liver dysfunction. In keeping with this line, the present study lands more weight on the argument against the fact that ivermectin is the drug of choice in parasitic infestation in sheep.

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تغير وظائف الكبد فى الكباش نتيجة للعلاج بالايفرميكتين

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أجرى هذا البحث على عدد ١٢ كبش برقى قسمت الى مجموعتين متساويتين. المجموعة الأولى أحتفظ بها كمجموعة ضابطة بينما حقنت المجموعة الثانية بجرعة قدرها ٢ر٠ مليجرام ايفرميكتين / كجم وزن حى تحت الجلد مرة واحدة .

وقد أظهرت المجموعة المعالجة بالايفرميكتين زيادة ملحوظة فى نشاط أنزيمات الترانسفيراز والارجنيز والسوربيتول ديهيدريجينيز والجلوسترات ديهيدوجينيز ومستوى كولسترول فى المصل. بينما لم يتأثر مستوى اليوريا أو الكريـاتنين نتيجة للعلاج بالايفرميكتين. ومن هنا يمكن أن نستنتج أن الايفرميكتين يحدث نوعا من الخلل الكبدى فى الكباش.