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Some clinico-pathological observations in Nubian goats treated with ivermectin

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L'ivermectine a été administrée en sous-cutanée à des chèvres de Nubie apparemment saines à la dose recommandée thérapeutiquement de 0,2 mg/kg et aux doses de 1 mg/kg et 5 mg/kg ; les variables cliniques, pathologiques, biochimiques et hématologiques ont été étudiées. A la dose de 0,2 mg/kg et 1 mg/kg, aucun signe clinique évident ni aucun changement hématologique, biochimique ou pathologique n'ont été observés, à l'exception de signes de douleur passagère à l'endroit de l'injection. Ces animaux ont été abattus une semaine après le traitement. Aucune modification macroscopique ou histopathologique n'a été relevée. Chez les quatre chèvres qui ont reçu une dose de 5 mg/kg, des signes d'intoxication sont apparus quelques minutes après le traitement, principalement d'ordre nerveux, se manifestant par une irritabilité, des mouvements rotatoires de la tête, des spasmes musculaires, l'agitation de la queue, la salivation, des bèlements excessifs, des gémissements, l'affaissement et finalement la mort. Une chèvre est morte dans les cinq minutes suivant le traitement, les trois autres dans les trois ou quatre jours suivants. Ces dernières avaient des taux cardiaques et respiratoires inférieurs à la normale, présentaient de l'anorexie et de l'anémie. A l'autopsie on a trouvé des hémorragies et des congestions dans le poumon et dans le foie. Aucun changement histopathologique majeur n'a été observé, à l'exception cependant d'une hépatite nécrosante non-suppurative multi-focale trouvée dans le foie. *Mots clés* : Chèvre de Nubie - Ivermectine - Anthelminthique - Toxicité - Soudan.

INTRODUCTION

Ivermectin is a relatively new antiparasitic agent, which is found to be effective against a wide array of organisms in a number of domestic animals (1, 4).

Although numerous papers have been published about the therapeutic usefulness of ivermectin, little or no work seems to have been reported about the toxicity of this drug in animals except in dogs, horses and tortoises (9, 12, 13, 15). After the completion of the present work, a paper investigating the toxicity of ivermectin in goats appeared (11).

In view of the fact that control over the purchase and use of veterinary drugs in most of the tropical coun-

tries is lax or non-existent, overdosage (and consequently toxicity) occurs commonly in animals. As the recommended dose of ivermectin is rather small, overdosage with this drug seems possible, particularly if the drug used (as is often the case) by non-professionals. Therefore it was thought of some interest to investigate the clinical, haematological and pathological effects which might occur following treatment of healthy goats with this drug at the recommended dose and above.

MATERIAL AND METHODS

Animals

Fourteen healthy Nubian goats of both sexes, one to three years old, and weighing 9 to 18 kg, were used in this study. They were housed in groups of three to four, and provided with green lucerne, sorghum grains and water *ad libitum*. The animals were acclimatized to their surroundings for three days before the start of the experiment.

Blood collection

At the start of the experiment and at intervals thereafter, blood (10 ml) was collected from the jugular vein using heparinized syringes. A portion of the blood (7 ml) was centrifuged at 900 g for 15 ml, and plasma separated and stored at -20 °C. The rest of the blood was immediately used for the haematological studies.

Treatment

Ivermectin solution (Ivomec[®], M.S.D., The Netherlands) was a gift from M.S.D. agent in Khartoum, Sudan. One group of animals (n = 3) received saline injections (1 ml) and served as controls. The second group (n = 3) received the drug at a dose of 0.2 mg/kg, which is the recommended therapeutic dose. The third group (n = 4) received 1.0 mg/kg, and the fourth group (n = 4) received 5 mg/kg. All the treatments were injected subcutaneously. The animals were observed after the treatment till death or killing.

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Haematological methods

The erythrocyte and leucocyte counts, packed cell volume (PCV) and haemoglobin concentrations were estimated by standard methods described by DACIE and LEWIS (6). Differential leucocyte counts were made using the battlement method.

Clinical methods

A thorough clinical examination was performed on the animals before and during the experiment. The examination was made by the same veterinarian and at about the same times each day. Parameters recorded included general state of the animal, gait, heart, pulse and respiratory rates. Rectal temperature was taken using a mercury thermometer.

Plasma biochemical methods

Sorbitol dehydrogenase (S.D.), glutamate oxaloacetate transaminase (G.O.T.) and glutamate pyruvate transaminase (G.P.T.) were determined by the methods of FORD (8), and BERGMAYER and BERNT (2, 3), respectively. Sodium (Na) and potassium (K) were measured by flame photometry. Creatinine, bilirubin and cholesterol were measured by the colorimetric methods of WHITE and FRANKEL (17), DANGERFIELD and FINLAYSON (7), and ZLATKIS, ZAK and BOYLE (18), respectively. Urea nitrogen and ammonia were determined by the methods of VARLEY (16) and CHANEY and MARBACH (5).

Pathological methods

After death or killing of animals, *post mortem* examination was conducted. Small pieces of some selected tissue (liver, different brain regions, kidney, heart, lung, skin, intestine, testes and spleen) were taken and placed in 10 p. 100 formol-saline. Sections were cut at 5 μ m thickness, embedded in paraffin wax, and stained with haematoxylin and eosin.

RESULTS

Clinical signs

The goats treated with ivermectin at doses of 0.2 or 1 mg/kg appeared clinically normal and remained so till they were killed one week after treatment. Only slight transient pain at the site of injection was observed. The four goats which were given the drug at

a dose of 5 mg/kg showed, two minutes after injecting the drug, signs of hyperexcitability, excessive tail wagging, salivation, moaning and vocalization, rotation of the head sideways, muscle spasms (especially in the hind limbs), sternal-belly recumbency, apparent blindness, coma, and finally death. The goat which was most affected died about five minutes after treatment. The rest remained affected. They became anorectic, anaemic, had ruminal stasis, and produced soft faeces. Rectal temperature, heart and respiratory rates increased slightly during the first 15 min. of treatment, then decreased below normal. The animals died within three to four days after treatment.

Haematological findings

No significant difference was found in the haematology between the control animals and those treated with ivermectin given at doses of 0.2 or 1 mg/kg ($P > 0.1$). The three animals which received the highest dose (and survived for three or four days) had lower erythrocyte counts, PCV, and Hb concentration on the 3rd day of treatment ($P < 0.05$) (Table I). Although platelet counts were not made, it was noticed that the platelets from goats on the highest dose of ivermectin appeared clumped.

Biochemical findings

The results are shown in table II. The treatment caused progressive increase in the activity of G.O.T. and S.D., but not G.P.T. which remained unaffected. There were significant increases in the plasma concentrations of urea nitrogen, ammonia and cholesterol. There were no significant effect on the concentrations of bilirubin, sodium, potassium or creatinine.

Pathological findings

No significant gross or histopathological changes were observed in goats treated with ivermectin at doses of 0.2 or 1.0 mg/kg. At a dose of 5.0 mg/kg moderate haemorrhage and congestion in the liver and lung were seen grossly in all four animals. Histopathologically, the liver had multi-focal non-suppurative necrotizing hepatitis. Diffuse hepatocellular cloudy swelling was also noted. The adventitia of some blood vessels (mostly veins) in the lung were slightly distended with eosinophilic oedematous fluids. In the small intestine, globular leucocytes were seen between the epithelial cells of the crypts and villi. In the skin (site of injection) there were hyperkeratosis in the epidermis, occasional ovoid masses of degenerated cells within the stratum corneum, and mild superficial perivascular dermatitis. The pulmo-

TABLE I The effect of ivermectin (5 mg/kg) on some haematological variables in the goat.

	Days of the experiment							
	Day 0		Day 1		Day 2		Day 3	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
Erythrocytes ($10^{12}/l$)	12.59 ± 1.9	12.11 ± 1.3	13.96 ± 1.1	12.00 ± 1.3	13.81 ± 1.7	11.22 ± 1.2	13.41 ± 1.3	9.31 ± 0.8(*)
Leucocytes ($10^3/l$)	11.20 ± 0.7	10.80 ± 0.8	10.20 ± 0.8	11.31 ± 0.9	11.21 ± 0.8	12.31 ± 3.1	11.31 ± 0.7	12.71 ± 1.1
PCV (p. 100)	29.3 ± 2.1	28.7 ± 2.1	30.3 ± 2.7	28.3 ± 3.1	29.3 ± 1.9	26.1 ± 1.9	30.5 ± 2.3	21.1 ± 2.4(*)
Hg (g/100 ml)	11.4 ± 1.7	11.0 ± 1.3	11.7 ± 1.8	10.3 ± 1.0	11.3 ± 1.8	9.1 ± 0.9	11.8 ± 1.4	8.9 ± 0.7(*)
Neutrophils (p. 100)	39.0 ± 4.2	33.9 ± 4.3	36.6 ± 3.6	38.5 ± 2.1	32.3 ± 3.2	35.5 ± 4.2	32.5 ± 4.1	38.7 ± 3.9
Esinophils (p. 100)	3.7 ± 0.3	4.5 ± 0.4	4.3 ± 0.5	4.7 ± 0.5	4.7 ± 0.5	3.9 ± 0.4	4.3 ± 0.5	4.7 ± 0.5
Lymphocytes (p. 100)	55.5 ± 5.1	59.5 ± 6.3	56.8 ± 4.8	53.7 ± 5.1	60.3 ± 5.7	55.3 ± 6.1	59.8 ± 4.9	53.7 ± 6.3
Monocytes (p. 100)	1.8 ± 0.7	2.1 ± 0.3	2.3 ± 0.4	3.1 ± 0.3	2.7	5.3 ± 0.5	3.4 ± 0.3	2.9 ± 0.31

The values are means ± s.e.m. (n = 3).

(*) P < 0.05 (unpaired t-test).

TABLE II The effect of ivermectin (5 mg/kg) on some plasma constituents of the goat.

	Days of the experiment							
	Day 0		Day 1		Day 2		Day 3	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
G.O.T. (U/L)	103.3 ± 11.2	109.3 ± 13.2	110.7 ± 13.2	137.8 ± 14.2	109.3 ± 14.2	201.2 ± 23.7(*)	113.7 ± 13.3	211.2 ± 22.5(**)
G.P.T. (U/L)	29.3 ± 5.1	27.7 ± 6.2	31.2 ± 3.2	39.3 ± 3.9	31.3 ± 4.2	32.1 ± 6.7	33.3 ± 3.2	42.3 ± 13.1
S.D. (U/L)	19.2 ± 3.9	17.2 ± 5.1	18.8 ± 2.7	30.1 ± 3.7(*)	17.7 ± 2.1	39.2 ± 3.9(*)	20.1 ± 2.5	45.3 ± 5.1(*)
Urea N ₂ (mmol/L)	11.8 ± 2.1	13.7 ± 3.1	12.1 ± 3.1	16.2 ± 2.7	12.9 ± 4.1	23.3 ± 2.1(*)	11.7 ± 2.1	24.1 ± 2.1(**)
Ammonia (mmol/L)	40.2 ± 6.1	39.3 ± 8.2	43.7 ± 4.1	49.2 ± 5.2	41.3 ± 5.1	62.3 ± 6.2(*)	43.2 ± 5.6	72.7 ± 7.9(**)
Bilirubin (μmol/L)	2.8 ± 1.3	2.0 ± 0.9	2.3 ± 0.9	2.5 ± 1.6	2.5 ± 1.0	2.7 ± 2.1	2.6 ± 0.9	2.9 ± 1.1
Cholesterol (mg/100 ml)	110.1 ± 14.2	120.1 ± 16.1	120.3 ± 15.1	144.2 ± 13.2	120.0 ± 13.1	157.3 ± 16.1	113.9 ± 13.2	162.1 ± 14.2(*)
Sodium (mmol/L)	138.0 ± 16.2	141.1 ± 15.1	139 ± 17.1	142.1 ± 13.9	129.9 ± 13.5	130.3 ± 15.1	136.2 ± 16.2	140.2 ± 15.2
Potassium (mmol/L)	3.3 ± 0.3	4.0 ± 0.5	3.5 ± 0.3	3.6 ± 0.4	3.9 ± 0.2	3.7 ± 0.4	3.7 ± 0.5	3.9 ± 0.4
Creatinine (μmol/L)	24.5 ± 2.5	25.2 ± 3.1	26.3 ± 3.0	27.7 ± 3.3	25.1 ± 2.7	24.4 ± 2.4	24.9 ± 2.3	27.1 ± 3.1

The values are means ± s.e.m. (n = 3-4).

(*) P < 0.05; (**) P < 0.01 (unpaired t-test).

nary parenchyma of two goats on the higher dose were atelectic.

No significant lesions were found in the brain, spleen, kidneys or testes.

DISCUSSION

The present results showed that ivermectin, at the recommended therapeutic dose, and at five times that dose, produced no serious untoward effects in Nubian goats. This finding agrees with that of NAJANJA *et al.* (11) for goats of East African breed. Recently, the

therapeutic usefulness of ivermectin in goats infested with gastrointestinal nematodes has been reported by SWAN and GROSS (14). These authors found no untoward effects in goats treated orally with ivermectin at doses ranging from 50 to 200 μg/kg.

The irritation produced at the site of injection caused transient signs of pain, but no serious gross of histopathological changes in goats receiving the low doses used. The irritation was reported to be due to the drug vehicle used (propylene glycol) and not to the drug itself (M.S.D. data, cited by NAJANJA *et al.*, 11).

Severe signs of acute toxicity were observed in goats treated with 25 times the therapeutic dose. These were mainly nervous in nature. The mechanism(s) by which the toxicity is produced is not known. It has been proposed that ivermectin acts by paralyzing nemato-

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des and arthropods by disrupting alpha-aminobutyric acid (GABA)-mediated transmission of nerve signals (4). It is possible that the high dose of ivermectin might act in a similar manner in treated animals, leading to affection of the nervous system.

The nervous signs produced by ivermectin could also have resulted from the liver affection. Hyperammoniaemia is a known cause of nervous signs. The liver lesion was reflected biochemically in the rise of G.O.T. and S.D. activities, and the concentrations of urea nitrogen, ammonia and cholesterol. The rise in the cholesterol might also be related to a possible « stressor » action of the drug resulting in the stimulation of the cortical adrenal gland. The mechanism(s) of toxicity of ivermectin in mammals warrants more investigations (10).

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Ivermectin was administered subcutaneously to healthy Nubian goats at the recommended therapeutic dose of 0.2 mg/kg and at doses of 1 mg/kg and 5 mg/kg, and various clinical, pathological biochemical and haematological variables studied. At a dose of 0.2 mg/kg and 1 mg/kg no obvious clinical signs, nor haematological, biochemical or pathological changes were observed, except for transient signs of pain at the site of injection. These animals were killed one week after treatment. No significant gross or histopathological changes were found. In four goats given a dose of 5 mg/kg, signs of toxicity were seen a few minutes after treatment. These were mainly nervous in nature and included irritability, rotation of the head sideways, muscle spasms, tail wagging, salivation, excessive vocalization, moaning, recumbancy and finally death. One goat died five minutes after treatment, while the other three died within three to four days. These animals had lower heart and respiratory rates than normal, were anorectic and became anaemic. On *post mortem* there were some haemorrhages and congestions in the lung and liver. No major histopathological changes were observed, however, except in the liver, where there was multi-focal non-suppurative necrotizing hepatitis. *Key words* : Nubian goat - Ivermectin - Anthelmintic - Toxicity - Sudan.

Because veterinary drugs in developing countries are not properly controlled, and could easily fall in the hands of non-professionals, there is a genuine concern that overdosing diseased animals may occur. This is particularly so in the case of drugs for which the recommended dose is rather small.

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ALI (B. H.), ABU SAMRA (M. T.). Observaciones clínicas y patológicas de cabras de Nubia tratadas con ivermectina. *Rev. Elev. Méd. vét. Pays trop.*, 1987, 40 (2) : 141-145.

Se administró ivermectina por vía subcutánea a cabras de Nubia al parecer sans a la dosis terapéutica recomendada de 0,2 mg/kg y a la dosis de 1 mg/kg y de 5 mg/kg ; Se estudiaron las variables clínicas, patológicas, bioquímicas y hematológicas. A la dosis de 0,2 mg/kg y de 1 mg/kg ningún síntoma clínico evidente y ninguna modificación hematológica, bioquímica o patológica ocurrieron con excepción de síntomas de dolor pasajeros al punto de inyección. Se mataron los animales una semana después del tratamiento. No se observó ninguna modificación macroscópica o histopatológica. En las 4 cabras que recibieron una dosis de 5 mg/kg, síntomas de intoxicación, principalmente nerviosos, aparecieron algunos minutos después del tratamiento con irritabilidad, movimientos rotatorios de la cabeza, espasmos musculares, agitación de la cola, salivación, balidos excesivos, gemidos, postración y al fin muerto. Una cabra murió cinco minutos después del tratamiento, tres demás durante los tres o cuatro días siguientes. Estas últimas tenían tasas cardíacas y respiratorias inferiores a la normal, presentaban anorexia y anemia. A la autopsia se observaron hemorragias y congestiones en el pulmón y en el hígado. No se notó ninguna modificación histopatológica importante a excepción de una hepatitis con necrosis y sin supuración multifocal en el hígado. *Palabras claves* : Cabra de Nubia - Ivermectina - Antihelmintico - Toxicidad - Sudán.

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