

The anthelmintic efficacy of d.l. Tétramisole (**) against *Haemonchus contortus* infection in goats

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RÉSUMÉ

IDRIS (UM EL ALIM A.), ADAM (S.E.I.), TARTOUR (G.). — Action anthelminthique du Tétramisole contre l'infection à *Haemonchus contortus* chez les chèvres. *Rev. Elev. Méd. vét. Pays trop.*, 1984, 37 (2) : 165-174.

Onze chèvres nubiennes ont été divisées en six groupes pour tester l'efficacité du Tétramisole contre *Haemonchus contortus*.

Les critères ont été l'aptitude à éliminer les parasites et leurs œufs et la comparaison histologique des changements de différents tissus et organes avant et après le traitement.

L'efficacité de cet anthelminthique est évidente après une dose orale unique de 40, 80 ou 240 mg par kg vif. Le comptage des œufs dans les fèces indique également la mort des parasites mais un retraitement est nécessaire après 3 semaines, même à la dose de 80 mg/kg pour éviter la réinfestation à partir d'individus immatures plus résistants que les adultes. Enfin, au-delà de cette dose, le Tétramisole est toxique chez la chèvre et, à 240 mg/kg, de graves troubles rénaux, hépatiques et cardiaques entraînent la mort.

Mots clés : Anthelminthique - Tétramisole - *Haemonchus contortus* - Chèvres - Soudan.

SUMMARY

IDRIS (UM EL ALIM A.), ADAM (S.E.I.), TARTOUR (G.). — The anthelmintic efficacy of d.l. Tetramisole against *Haemonchus contortus* infection in goats. *Rev. Elev. Méd. vét. Pays trop.*, 1984, 37 (2) : 165-174.

Eleven nubian goats were divided in six groups for testing the efficiency of Tetramisole against *Haemonchus contortus*. The criteria were the ability to eliminate both parasites and eggs and the analysis of the histological comparison of changes in different organs and tissues ex-ante and ex-post treatment.

The anthelmintic efficiency is evident and worms disappear after a single oral dose of 40, 80 and 240 mg per live kg. Faecal egg counts indicates suppression of parasites, but retreatment is recommended after three weeks even at 80 mg/kg dosing to avoid reinfestation from immatures more resistant than adults to the drug. Beyond this figure, Tetramisole is toxic to goats, and at 240 mg/kg, severe renal and hepatic insufficiencies occur with death as consequence.

Key words : Anthelmintic - Tetramisole - *Haemonchus contortus* - Goats - Sudan.

INTRODUCTION

Most of the nematode parasites found in goats are as susceptible to anthelmintic drugs as those found in sheep. For example, thiabendazole (*) is effective in eliminating *Haemonchus* and *Strongyloidea* infections in sheep (KELLY and WHITLOCK, 1975 ; ADAM, unpublished data).

From time to time new anthelmintic drugs, such as d.l. tétramisole (**) are synthesized, but information on their anthelmintic activity against experimental haemonchosis and on the side effects of the drug is still lacking in goats. The present experiments were designed to investigate these factors.

(**) Stronmisole, trade name contains 20 p. 100 of d.l. tétrahydro-2,3,5,6 phényl-6-imidazole (2-1.b.) thiazole base as hydrochloride or Tetramisole.

(*) Generic name : 2-(4-Thiazolyl) - 1 H benzimidazole.

The criteria used for the evaluation of this antinematodal compound included the ability of the drug to eliminate *Haemonchus contortus* and the effect of treatment on pathologic changes in different organs and tissues caused by *Haemonchus* infection.

MATERIALS AND METHODS

Experimental design

Eleven 6 to 14 month-old nubian goats of both sexes were used for the study. The animals were divided into six groups as follows : Goats 1 and 2 were orally infected with 280 and 800 infective *Haemonchus* larvae, respectively, (group I). Goats 3 and 4 were each infected with 300 *Haemonchus* larvae and were then dosed orally, 46 days from the date of infection with Tetramisole given in an oral single dose of 40 mg/kg (group II). Goats 5 and 6 were each infected with 280 infective *Haemonchus* larvae and were then dosed on day 46 with Tetramisole given in a single dose of 80 mg/kg (group III). Goat 6 was retreated 21 days later. Goats 7 and 8 were each infected with 200 infective *Haemonchus* larvae and were then dosed on day 35 with Tetramisole given in a single dose of 240 mg/kg (group IV). The uninfected goat 9 was given stromisole at 240 mg/kg/day for three consecutive days (group V). Tetramisole was dissolved in tap water. Goats 10 and 11 were kept as untreated uninfected controls (group VI). All animals were maintained on lucerne and allowed free access to drinking water.

Source of infection

Faeces were collected from goats naturally infected with *Haemonchus contortus* in clean petri-dishes. The animals were either reared at the University Farm in Khartoum-North or admitted to the Department of Veterinary Clinical Studies, University of Khartoum for examination. The faecal samples were sealed and immediately taken to the laboratory for examination.

Faecal-egg count

The method described by SOULSBY (12) was used for counting the eggs in samples of faeces of the infected animals.

Hatching of eggs

The method used for hatching of *Haemonchus* eggs was described by BODDIE (1969). The infective *Haemonchus* larvae were

counted according to the method described by DOWNEY and CONNOLLY (4).

Method of infection

The infective larvae in MaCartney bottles were given by the oral route to the experimental animals.

Commencing 15 days after infection, examination of faeces for *Haemonchus* eggs took place every week. Faeces were collected from animals and faecal egg counts were carried out every week for a period of 10 weeks.

The method used for testing the viability of eggs was described by KAGAN and PELLEGRINO (9). The adult *Haemonchus* worms were recovered from the abomasae of goats and separated into males and females according to the method described by SOULSBY (2).

Histological methods

At necropsy, samples of the abomasum, intestines, liver, kidney, heart, lungs and spleen were fixed in 10 p. 100 formol-saline. 6 µm thick sections were prepared and stained with haematoxylin and eosin (H & E), the periodic acid-Schiff (PAS) method, Perl's prussian blue, Masson's trichrome, Gordon and Sweet's and Lillie's methods.

Chemical methods

Blood samples collected from goats by jugular venipuncture before and during the experiment were allowed to clot and the sera were analysed for the activities of aspartate amino-transferase (GOT) and alanine amino-transferase (GPT) by the method of REITMAN and FRANKEL (11) and for the concentrations of total protein by the biuret method, bilirubin by the method of DANGERFIELD and FINLAYSON (3), ammonia by the method described by VARLEY (13), urea and creatinine by the methods of WHITE and FRANKEL (14). Calcium and magnesium by the methods of FRANKEL and REITMAN (6) and sodium and potassium by flame photometry as described by VARLEY (13).

Haematological methods

Samples of blood were collected from goats by jugular vein puncture into clean dry bottles containing the disodium salt of ethylene diamine tetraacetic acid (EDTA) as anticoagulant. Packed cell volume (PCV) was measured in a microhaematocrit centrifuge (HAWKSLEY and SONS Ltd., England).

TABLE N° I-Efficacy of Stronmisole in the treatment of *Haemonchus contortus* infection in goats

Group	Goat N°	Age (months)	Sex	N° of <i>Haemonchus larvae</i> given	Oral dose of Stronmisole (mg/kg)	Total amount of Stronmisole (g)	Day dosed with Stronmisole	Day killed	N° of adult <i>H. contortus</i> recovered	
									Female	Male
I (infected control)	1	9	M	280	-	-	-	40	55	19
	2	9	M	800	-	-	-	30	210	107
II	3	7 1/2	M	300	40	0.380	46	63	Nil	
	4	6	M	300	40	0.4	46	57	Nil	
III	5	7 1/2	M	280	80	1.2	46	70	Nil	
	6	7 1/2	F	280	80	1.2	46	70	Nil	
IV	7	8	M	200	240	2.88	35	42	Nil	
	8	8	M	200	240	2.88	35	42	Nil	
V	9	9	F	Nil	720	7.2**	0	15	Nil	
VI (untreated un- infected controls)	10	14	M	Nil	-	-	-	36	Nil	
	11	6	M	Nil	-	-	-	36	Nil	

** Stronmisole was given to goat 9 for three consecutive days.

Haemoglobin concentration (Hb) was determined by the cyanmethaemoglobin technique with an haemoglobin meter (Evans Electro-selenium Ltd., England). Red and white blood cells (RBC and WBC) were counted in improved Neubauer haemocytometers. Mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC) were calculated from RBC, PCV and Hb values.

RESULTS

Clinical findings

Goats 1 and 2 (group I) which received single doses of 280 and 800 infective *Haemonchus* larvae, respectively, showed inappetence, dullness and diarrhoea on day 15. Thereafter, the animals had a rough coat and pale mucous membranes and became recumbent and were slaughtered on days 40 and 30 respectively. In goats 3 and 4 (group II), there were soft faeces, inappetence and depression between days 21 and 29. When Tetramisole was given in a single dose of 40 mg/kg, on the 46th day of the experiment, there was a slight clinical improvement and the goats were killed on days 63 and 57 (17 and 11 days after dosing respectively). Goats 5 and 6 (group III) showed signs of haemonchosis on day 21 and their health improved following the treatment with Tetramisole at 80 mg/kg on day 46. The animals were killed on day 70 (24 days after dosing). When the drug was given to goats 7 and 8 (group IV) in a single dose of 240 mg/kg, on day 35, the general

condition of the animals deteriorated and there was severe diarrhoea and ataxia. The goats were killed on day 42 (7 days after dosing). Goat 9 (group V) which received stromisole at 240 mg/kg/day for three consecutive days showed diarrhoea, salivation, inappetence, marked depression and recumbency and was killed on day 15. The untreated uninfected control goats 10 and 11 (group VI) showed no clinical changes and were killed on day 36.

Parasitological findings

Table I shows that 280 or 800 infective *Haemonchus* larvae given to goats 1 and 2 (group I) produced in the abomasum at post-mortem, 74 and 317 adult worms of both sexes, respectively. No adult *Haemonchus* worms were found in the abomasae of goats 3, 4 (group II), 5 (group III), 7 and 8 (group IV) all of which received a single oral treatment at dose rates of 40, 80 and 240 mg/kg, respectively. In goat 6 (group III) which received a second dose of 80 mg/kg 21 days after the initial dose of the drug, infection with *H. contortus* was completely eliminated.

The faecal egg counts for the infected and treated goats are shown in Table II. In the untreated infected control goats 1 and 2 (group I), the faecal egg counts reached a peak of 1 400 and 6 000 e.p.g. at weeks 6 and 4, respectively. There was a 100 p. 100 reduction in the number of *H. contortus* eggs in faeces of goats in groups II, III and IV, 7 days after treatment at doses of 40, 80 and 240 mg/kg, respectively. The examination of faeces from goat 6 (group III) revealed *Haemonchus* eggs

TABLE N°II-Faecal egg and viability in infected and treated goats

Group	Goat N°	N° of larvae given	N° of eggs per g of faeces/week								Percentage viability		
			2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Before treatment	After treatment
I	1	280	Nil	1000	1200	1400						60	
	2	800	Nil	4000	6000							70	
II	3	300	Nil	Nil	800	800	1200*	Nil	Nil			50	Nil
	4	300	Nil	Nil	Nil	400	800*	Nil	Nil			65	Nil
III	5	280	Nil	1000	1600	1400	600*	Nil	Nil	Nil	Nil	72	Nil
	6	280	Nil	400	1100	1200	1200*	Nil	Nil	400	Nil	60	20
IV	7	200	Nil	Nil	600*	Nil						50	Nil
	8	200	Nil	Nil	600*	Nil						40	Nil

* Dosed with anthelmintic.

(400 e.p.g.), 21 days after dosing. The goat was given a second dose of 80 mg/kg of stromisole on day 67 and was killed on day 70 (24 days after the first dose).

The results of hatching of *Haemonchus* eggs from infected goats showed that the viability of eggs in the faeces ranged from 40-72 % and that of eggs from treated goat 6 was 20 % (Table II).

The untreated uninfected control goats 10 and 11 (group VI) showed no evidence of *Haemonchus* infection.

Post-mortem findings

The post-mortem findings in the infected and treated goats are summarized in Table III. In the untreated infected goats 1 and 2 (group I), there were petechial haemorrhages and erosions in the abomasal mucosa, hydropericardium, hydroperitoneum, gelatinization of the renal pelvis and epicardial fat and swelling of the hepatic lymph nodes. The renal cortex and liver appeared pale yellow in colour. The hepatic, renal and abomasal lesions were less marked in goats 3, 4 (group II), 5 and 6 (group III). In goats 7 and 8 (group IV) and 9 (group V), there were ecchymotic and/or diffuse haemorrhages in the endocardium, renal cortex and abomasal mucosa. The liver was congested and the peritoneal cavity contained sanguineous fluid. There were no changes in the untreated uninfected control goats 10 and 11 (group VI).

Histological findings

In goats in group I, there were haemorrhages, congestion and infiltration of mononuclear cells in the *lamina propria* and focal loss of the epithelial cells of the mucous membrane of the abomasum (Fig. 1), catarrhal enteritis, cytoplasmic vacuolation of the centrilobular hepatocytes and congestion of the hepatic sinusoids, haemorrhage in the renal glomeruli and focal degeneration of the cells of the convoluted tubules. In goats in groups II and III, the abomasal lesions were less marked and the number of mononuclear cells in the hepatic portal tracts and vacuolated hepatocytes was reduced. The renal convoluted tubules were dilated and the glomeruli contained an increased number of endothelial cells. In goats in groups IV and V, there was catarrhal abomasitis and enteritis, focal hepatocellular necrosis and fatty change and infiltration of the portal tracts with mononuclear cells, congestion and haemorrhage in the renal medulla and focal myocardial degeneration.

Changes in serum constituents

There were no significant changes in the activity of GPT and in the concentrations of bilirubin, calcium and magnesium in the serum of any of the goats. Goats in group I were exemplified by goat 1 which was killed on day 40. The activity of GOT and the concentration of sodium had risen on the 13th day and

TABLE N°III-Assessment of the findings at necropsy of infected and treated goats

Site	Finding	Group					
		I	II	III	IV	V	VI
Abomasum	Catarrhal abomasitis	+++	++	+	+	+	(-)
	Petechial haemorrhage in the abomasal mucosa	+	+	(-)	++	++	(-)
Small intestine	Focal catarrhal enteritis	++	+	+	+	+	(-)
Liver	Focal fatty charge and congestion	++	+	+	+++	+++	(-)
Kidney	Fatty change and haemorrhage in the renal cortex	+	+	+	++	++	(-)
	Gelatinization of the renal pelvis	++	+	(-)	(-)	(-)	(-)
Heart	Endocardial haemorrhage	(-)	(-)	(-)	+++	+++	(-)
	Gelatinization of the epicardial fat	++	+	(-)	(-)	(-)	(-)
	Hydropericardium	++	+	(-)	(-)	(-)	(-)
Peritoneal cavity	Hydroperitoneum	++	+	+	+++	+++	(-)

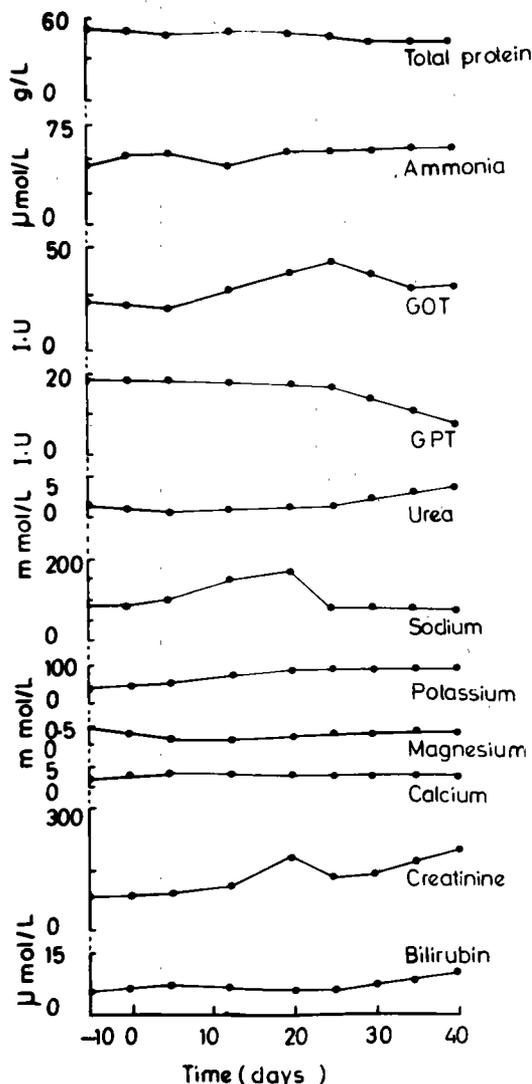
+ — +++, increasing severity of lesions ; (-), absence of lesions ; %, sanguineous fluid was found in the peritoneal cavity of goats in groups IV and V.



Fig. 1. — Catarrhal abomasitis and erosions of the abomasal mucosa in goat 2 in group I, orally infected with 800 *Haemonchus* larvae. H & E \times 120.

reached peaks on the 25th and the 20th days respectively. The activity of GOT was slightly raised at the time of slaughter (Fig. 2). The concentrations of sodium and total protein fell between days 25 and 40. Creatinine and urea showed slightly raised terminal concentrations. Animals of group II were exemplified by goat 3 which was killed on day 63 (17 days after dosing). The activity of GOT commenced to rise on day 20 and fluctuated above normal before treatment (Fig. 3). Thereafter, the enzyme activity was slightly above normal levels. The concentration of total protein fell between days 20 and 45 and had risen after treatment. The concentration of sodium had risen between days 20 and 45 and then fell to slightly above normal. Creatinine and potassium showed small increases terminally. In goat 6 (group III), there were increases in the activity of GOT and in the concentrations of creatinine, potassium and sodium and decreases in the concentration of total protein before treatment. Thereafter, the concentration of protein progressively increased from the second week after administration and GOT, potassium, sodium and creatinine gradually decreased during the same period

Fig. 2. — Changes in the activities of GOT and GPT and in the concentrations of total protein, total bilirubin, calcium, magnesium, ammonia, urea, creatinine, sodium and potassium in the serum of goat 1 in group I, infected with 280 *Haemonchus* larvae on day 0.



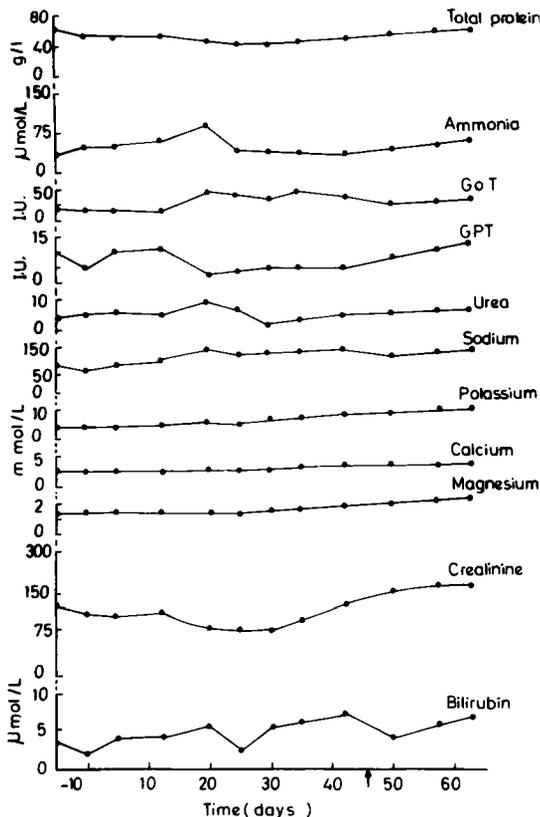


Fig. 3. — Changes in the concentrations of total protein, total bilirubin, urea, ammonia, creatinine, magnesium, calcium, sodium and potassium and in the activities of GOT and GPT in the serum of goat 3 in group II, infected with 300 *Haemonchus* larvae on day 0 and treated with a single dose of 40 mg/kg of strontisole on the day indicated by the arrow.

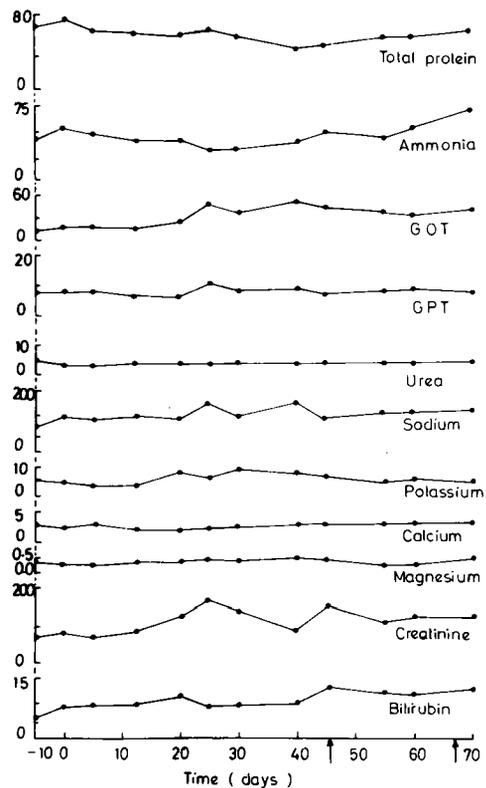


Fig. 4. — Changes in the activities of GOT and GPT and in the concentrations of total protein, total bilirubin, urea, ammonia, creatinine, magnesium, calcium, sodium and potassium in the serum of goat 6 in group III, infected with 280 *Haemonchus* larvae on day 0 and treated with a single dose of 80 mg/kg of strontisole on the day indicated by the arrow.

(Fig. 4). The concentration of ammonia was slightly high at the time of slaughter. In goats 7 (group IV) and 9 (group V), there were terminal increases in the concentrations of ammonia, potassium and creatinine and in the activity of GOT (Figs. 5 and 6). Total protein showed a reduced concentration terminally.

There were no changes in serum constituents of the untreated un-infected control goats 10 and 11 (group VI).

Hematological findings

The untreated infected control goat 1 was typical of group I. The PCV, RBC and Hb fell and were below preinfection levels between days 30 and 40 (Fig. 7). In goat 5 (group III), the RBC, Hb, PCV and MCV fell after infection with *H. contortus* larvae and rose to preinfection levels following treatment

(Fig. 8). The haematological changes observed in goats 3, 4 (group II) and 6 (group III) resembled those described for goat 5. The RBC counts, PCV, Hb, MCV and MCHC in the untreated uninfected control goats 10 and 11 (group VI) did not change. There were no significant changes in the total number or proportion of white blood cells in any goat.

DISCUSSION

The results of this experiment indicate that Nubian goats are susceptible to infection with *H. contortus* and that the parasite produces changes mainly in the abomasum. The main signs in infected goats are depression, soft faeces and loss of condition. These signs were

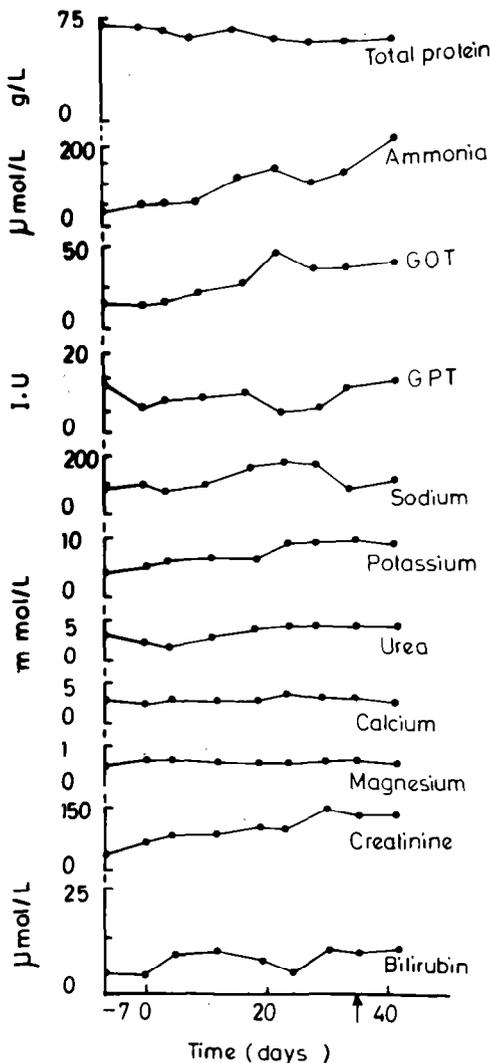


Fig. 5. — Changes in the activities of GOT and GPT and in the concentrations of total protein, total bilirubin, urea, ammonia, creatinine, magnesium, calcium, sodium and potassium in the serum of goat 7 in group IV, infected with 200 *Haemonchus* larvae and treated with a single dose of 240 mg/kg of stronmisole.

generally similar to those described in sheep infected with other gastro-intestinal helminths (7). It appears that at levels of infection between 200 and 800 infective *Haemonchus* larvae, the worms can achieve their potential of egg laying within 3-4 weeks post-infection. The viability tests on eggs of the parasite indicate that goats are susceptible hosts for *H. contortus*. The development of soft faeces may be due to catarrhal abomasitis and enteritis. The intestinal, hepatic and renal lesions may be due to toxins produced by the parasite.

The anthelmintic efficacy as assessed by removal of worms was high at single oral

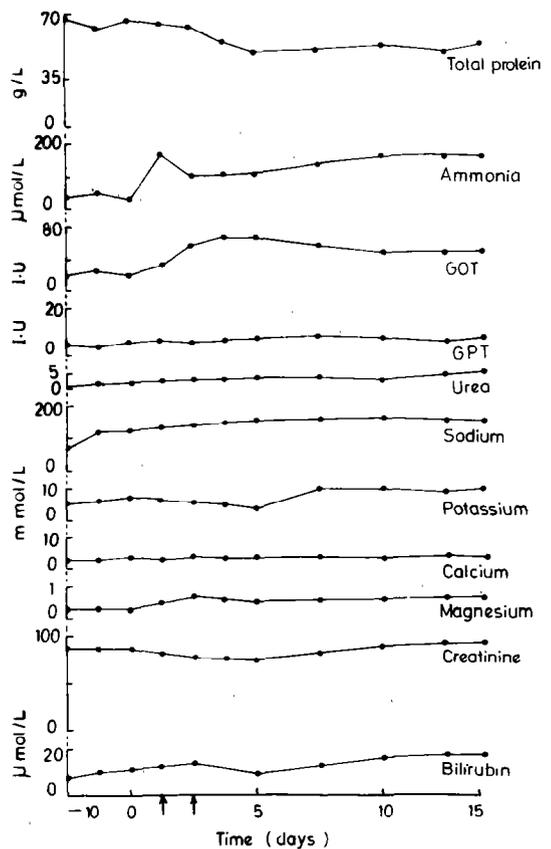


Fig. 6. — Changes in the activities of GOT and GPT and in the concentrations of total protein, total bilirubin, ammonia, calcium, creatinine, sodium, potassium and urea in the serum of goat 9 in group V, orally dosed with 720 mg/kg of stronmisole for 3 consecutive days.

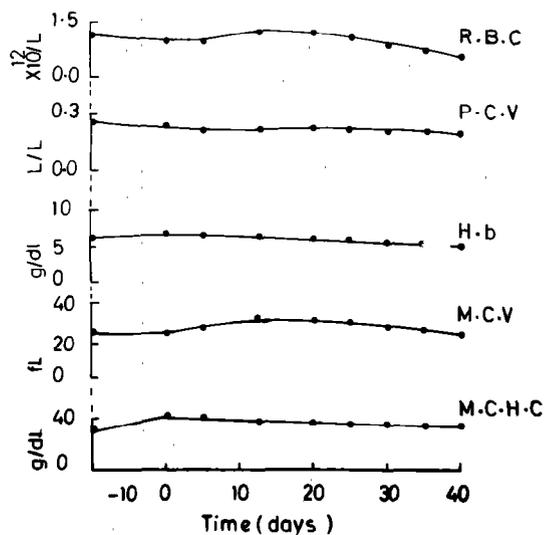


Fig. 7. — Changes in the red cell parameters in goat 1 in group I orally infected with 280 *Haemonchus* larvae on day 0.

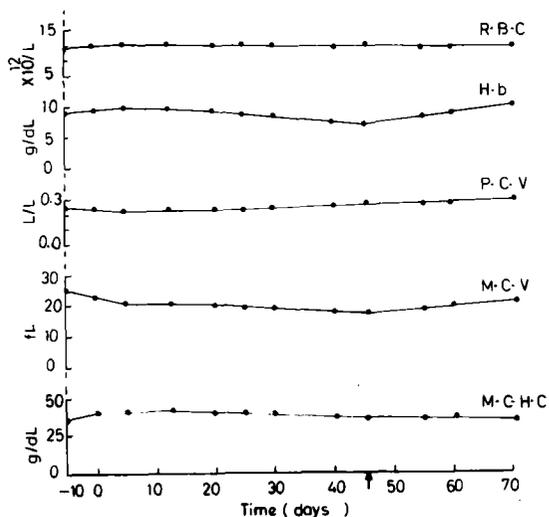


Fig. 8. — Changes in the red cell parameters in goat 5 in group III during infection with *H. contortus* larvae and stromisole treatment.

doses of 40, 80 and 240 mg/kg and post-treatment faecal egg counts indicated that production was completely suppressed. However, one of the goats treated in a single dose of 80 mg/kg passed *Haemonchus* eggs in the faeces 21 days after the dosing. The animal was then given a second dose. This finding indicates that retreatment in 3 weeks is recommended for the most effective therapy. In general, helminths are less susceptible to anthelmintics when immature (8).

Tetramisole in single or multiple doses of 240 mg/kg is toxic to goats and causes severe

diarrhoea, weakness of the hind limbs, salivation, and recumbency. The lesions are haemorrhages in the endocardium, renal cortex and medulla and abomasal mucosa, hepatic fatty change, necrosis and congestion and sanguineous fluid in the peritoneal cavity. The high serum GOT activity and ammonia and potassium concentrations and the fall in serum protein concentration may be due to both renal and hepatic insufficiency. The damage to the alimentary tract could have contributed to raised ammonia and GOT levels. Indeed, the concentration of GOT in the tissues of ruminant animals other than the liver is high (2,5).

It would appear from this experiment that *H. contortus* infection in goats can be of economical importance and that significant tissue damage and anaemia are produced. Although the anthelmintic efficacy in single doses of 40 and 80 mg/kg against *Haemonchus contortus* was high, retreatment in 3 weeks is necessary for the most effective therapy.

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RESUMEN

IDRIS (UM EL ALIM A.), ADAM (S.E.I.), TARTOUR (G.). Acción antihelmíntica del Tetramisole contra *Haemonchus contortus* en las cabras. *Rev. Elev. Méd. vét. Pays trop.*, 1984, 37 (2) : 165-174.

Se distribuyeron once cabras nubienses en seis grupos para comprobar la eficacia del Tetramisole contra *Haemonchus contortus*. Los criterios fueron la aptitud para eliminar los parásitos y sus huevos y la comparación histológica de las modificaciones de diferentes tejidos y órganos ante y después del tratamiento.

La eficacia de dicho antihelmíntico es evidente después

de una dosis oral única de 40, 80 o 240 mg/kg de peso vivo. La numeración de los huevos en las heces indica también la muerte de los parásitos pero se necesita un nuevo tratamiento después de 3 semanas, hasta con la dosis de 80 mg/kg para evitar la reinfestación a partir de parásitos inmaduros más resistentes que los adultos. Por último, más allá de esta dosis, el Tetramisole es tóxico en la cabra y, con 240 mg/kg, graves desórdenes renales, hepáticos y cardiacos causan la muerte.

Palabras claves : Antihelmíntico - Tetramisole - *Haemonchus contortus* - Cabras - Sudan.

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