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The effect of mebendazole and praziquantel on the cysts of *Echinococcus granulosus, Taenia hydatigena* and *T. ovis* in sheep

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SUMMARY

When administered orally at 50 mg/kg live weight to sheep for 14 days mebendazole killed almost all *Taenia hydatigena* and *T. ovis* cysts and significantly retarded the growth of *Echinococcus granulosus* cysts. A single subcutaneous injection of mebendazole at 50 mg/kg was ineffective and was only partially effective when injected at this rate into the peritoneal cavity. The lack of effect was attributed to the slow solubilization of the injected depot.

Praziquantel injected subcutaneously at 50 mg/kg disappeared from the injection site within three weeks. **All *T. hydatigena* cysts were killed in sheep harbouring up to 100 cysts, but not in those with more than this number. All *T. ovis* cysts were apparently killed. This drug had no effect on *E. granulosus*.**

The lethal effect of intraperitoneally injected mebendazole, and of praziquantel, on *T. hydatigena* cysts was related to the biomass of cysts.

INTRODUCTION

Several recently-developed broad-spectrum anthelmintics have been shown to damage the cysts of some cestodes in laboratory animals and pigs[2] [3] [4] [5] [6] [9] [10] [11] [12] [13] [14] [15] [18] [19] [22]. Two of these anthelmintics, mebendazole and praziquantel, have shown more promise than others. Their characteristics and biochemical effects have recently been described[1] [8] [17] [20] [21] [23]. Problems have arisen in applying these anthelmintics to the larval cestodes infesting sheep. It is impractical to medicate grazing sheep for extended periods; a necessary requirement for the maintenance of high levels of anthelmintic around the tissue-dwelling cysts. It is also difficult to infect sheep with a standard known number of cestode larvae, and moreover, especially with *Taenia ovis* larvae, it is difficult to guarantee the viability of these larvae in control animals during the period of anthelmintic treatment.

The effect of an extended oral dosing regime with mebendazole was compared with one parenteral injection of either mebendazole or praziquantel. Parenteral injections had previously been found to be effective in laboratory animals[11], and could be the best method for use in a field situation with sheep.

MATERIALS AND METHODS

Anthelmintics

Mebendazole was obtained in the pure crystalline form from Ethnor Pty. Ltd. The micronized hydrophobic powder was either wetted with a few drops of Triton X-100 in water and suspended at 100 mg/ml by gentle agitation, or was made into a relatively stable suspension of 100 mg/ml in 20% Chremaphor E.L. (BASF) in water. For oral administration a stable 5% suspension of mebendazole (Telmin R.L.T. Sheep Drench) was used.

Prazinquantel (Embay 8440) was obtained from Bayer-Leverkusen as the pure crystalline compound, and as a 2.5% injectable solution. Since the drug is metabolized rapidly by the liver, praziquantel was injected subcutaneously. The drug was suspended in a carrier so that a depot was created. Sufficient of the pure compound was suspended in the injectable solution to make a stable suspension containing 125 mg/ml.

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Routes of Application of Anthelmintics

Subcutaneous injection of mebendazole. Twenty-six weaned Romney lambs were obtained at 4 months of age. Six were autopsied immediately, and none contained any larval cestodes. Fourteen lambs were each injected subcutaneously over the left and right rib area with a total of 50 mg/kg body weight of pure mebendazole wetted with Triton X-100 and suspended in water. Six lambs remained uninjected. The lambs were then placed on a pasture known to be lightly contaminated with *Taenia hydatigena* eggs. Half the treated and control lambs were autopsied 2 months later, and the remainder 5 months after injection.

Subcutaneous injection of praziquantel and intraperitoneal injection of mebendazole. Twelve 6-months-old Romney lambs were divided into 4 equal groups. Lambs in Group 1 received an intraperitoneal injection of mebendazole in 20% Chremaphor E.L., while lambs in Group 2 received an intraperitoneal injection of the commercially available 5% suspension. Group 3 lambs received an intraperitoneal injection of mebendazole suspended in water, and Group 4 lambs received a subcutaneous injection of praziquantel in a site over the left rib area.

All formulations were administered at a rate of 50 mg active principle per kg live weight. For intraperitoneal injections lambs were suspended by their back legs and the injection was made in the inguinal region sagittal to the mid-line.

Effect of Mebendazole and Praziquantel on Cysts of *T. hydatigena, T. ovis* and *Echinococcus granulosus*

Eighty-eight Romney lambs were obtained within a week of birth. Fifty-eight lambs were each infected orally at 3 months of age with 1000 freshly-collected eggs of each of *T. hydatigena, T. ovis* and *Echinococcus granulosus*. The other 30 lambs each received 1000 eggs of each of *T. ovis* and *E. granulosus*. Three months later, the lambs were divided into 4 groups, as shown in Table II. Lambs in Group 1 did not receive either ... ielmintic. Group 2 lambs were given orally 50 mg/kg mebendazole each day for 14 days, in the form of the 5% stable suspension. Group 3 lambs received a single intraperitoneal injection of 50 mg/kg of mebendazole suspended in 20% Chremaphor E.L., and Group 4 lambs received a subcutaneous injection of 50 mg/kg of praziquantel.

All animals harbouring the three species of cysts were autopsied 6 weeks after the end of anthelmintic treatment, but those lambs only having *E. granulosus* and *T. ovis* were left for 5 months before autopsy. This enabled the effects of the drugs on *E. granulosus* cysts to be more easily assessed.

At autopsy representative samples of living and dead cysts were preserved in a solution of 4% formaldehyde in Krebs-Ringer phosphate, pH 7.2. At the 6 weeks autopsy the peritoneal cavity and viscera were searched for *T. hydatigena* cysts, and only the lungs were examined for *E. granulosus* cysts because of the overwhelming damage caused to the liver by the migratory larvae of *T. hydatigena*. At the 5 month autopsy both the liver and lungs could be accurately assessed for the number and size of *E. granulosus* cysts present. *E. granulosus* cysts were counted in liver tissue after making 2 mm slices, and in the lungs after slicing at 5 mm intervals. The condition of all cysts was evaluated visually, and the average dimensions of 10 randomly selected cysts were measured with vernier calipers. The musculature of the carcase was sliced at 3 mm intervals and inspected for *T. ovis* cysts.

All cystic lesions, except those preserved for histology, were sliced open to determine the viability of the enclosed larva. Preserved speciments were embedded in paraffin, sectioned at 7μm and stained with haematoxylin and eosin.

Effect of Mebendazole and Praziquantel on Cysts of *T. ovis*

Twenty 5-month-old Romney lambs were each infected orally with 2000 freshly collected *T. ovis* eggs. Eight weeks later the lambs were divided into 4 equal groups, and received mebendazole or praziquantel as previously described (Table IV). All lambs were autopsied 6 weeks after the initiation of anthelmintic treatment.

TABLE I: FATE OF MEBENDAZOLE INJECTED SUBCUTANEOUSLY INTO SHEEP AT 50 mg/kg BODY WEIGHT

Injected Sheep	Autopsied after 2 months			Autopsied after 5 months		
	Remains of drug	*T. hydatigena* larvae		Remains of drug	*T. hydatigena* larvae	
		Live	Dead		Live	Dead
1	++	1	0	+	1	2
2	++	0	2	–	0	0
3	++	1	0	+	2	0
4	++	0	3	–	1	1
5	++	0	1	+	1	5
6	++	1	0	+	0	0
7	++	1	0	+	0	2
Control Sheep						
1		2	0		0	3
2		1	1		2	0
3		1	0		2	0

++ = almost all drug still remains
+ = some drug remains
– = no drug remains

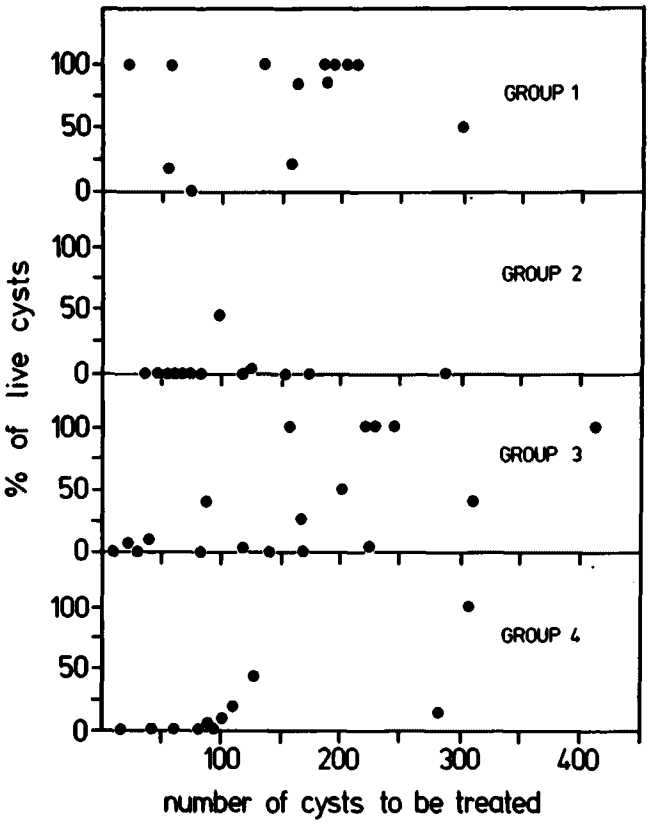

Fig. 1: *The survival of* Taenia hydatigena *cysts in lambs after various anthelmintic treatments. Each spot represents the data for one lamb.*
Group 1. No treatment.
Group 2. 50 mg/kg mebendazole orally each day for 14 days.
Group 3. 50 mg/kg mebendazole injected intraperitoneally.
Group 4. 50 mg/kg praziquantel injected subcutaneously.

RESULTS

Subcutaneous Mebendazole

Almost all lambs acquired some *T. hydatigena* from the infected pasture, and the development or survival of the larvae was not affected by the existence of a subcutaneous depot of mebendazole. The results are presented in Table I. The amount of drug remaining was estimated visually. Very little drug was

TABLE II: NUMBER OF LIVE AND DEAD CESTODE CYSTS FOLLOWING TREATMENT OF LAMBS WITH MEBENDAZOLE OR PRAZIQUANTEL

AUTOPSY 6 WEEKS AFTER TREATMENT

Treatment	Group No.	Lamb No.*	*T. hydatigena* mean numbers		*T. ovis* mean numbers		*E. granulosus* mean numbers
			Live	Dead	Live	Dead	live or dead in lungs
Control	1	13	116 (78)†	33 (50)	10 (19)	22 (20)	63 (34)
Mebendazole for 14 days	2	13	4 (13)	102 (68)	4 (9)	17 (29)	59 (46)
Mebendazole once intraperitoneal	3	18	89 (122)	72 (73)	2 (6)	24 (31)	86 (79)
Praziquantel once subcutaneous	4	11	40 (92)	79 (62)	3 (9)	15 (23)	79 (44)

AUTOPSY 22 WEEKS AFTER TREATMENT

Treatment	Group No.	Lamb No.	*T. hydatigena* mean numbers		*T. ovis* mean numbers		*E. granulosus* mean numbers
			Live	Dead	Live	Dead	live or dead in lungs and liver
Control	1	8	–	–	0.5(1.4)	3.3(4.0)	341 (153)
Mebendazole for 14 days	2	8	–	–	0	16 (24)	228 (125)
Mebendazole once intraperitoneal	3	7	–	–	0.3(0.8)	7 (6)	318 (134)
Praziquantel once subcutaneous	4	7	–	–	0	7 (12)	270 (76)

† Numbers in brackets are standard deviation of means.
– = Lambs were not infected with *T. hydatigena* cysts.
* Three lambs died approximately 3 weeks after infection, apparently from liver damage associated with the migrating larvae of *T. hydatigena*.

mobilized from the depot after 2 months and about half the drug was still present in 5 out of 7 lambs 5 months after injection. The 6 control lambs all showed extensive diarrhoea throughout the experimental period, a condition that responded for a short time to treatment of the whole flock with the anthelmintic thiabendazole at the dosage recommended for the control of gastrointestinal parasites. In contrast, the injected lambs never showed diarrhoea for the duration of the experiment.

Subcutaneous Praziquantel and Intraperitoneal Mebendazole

Mebendazole as the stable 5% suspension appeared to be slowly mobilized from the peritoneal cavity, and caused extensive adhesions of the viscera. Most mebendazole in 20% Chremaphor E.L. or in water had disappeared from the peritoneal cavity after three weeks, and only minor adhesions resulted. The drug in 20% Chremaphor E.L. was the formulation of choice, because of the difficulty of administering a known amount of drug suspended temporarily in water.

Praziquantel caused some subcutaneous inflammation around the injected depot, but no necrosis or adhesion remained when all the drug finally disappeared after 3 weeks.

Effect of Mebendazole and Praziquantel on Cysts of *T. hydatigena, T. ovis* and *E. granulosus*

The results are summarised in Tables II, III, IV and V, and in Figure 1.

T. hydatigena cysts. The 14-day oral mebendazole treatment was very effective, all cysts being killed in most animals (Fig. 1). The percentage of cysts surviving following intraperitoneal injection of mebendazole or subcutaneous injection of

TABLE III: MEAN SIZE OF *E. GRANULOSUS* CYSTS FOUND IN LAMBS FIVE MONTHS AFTER TREATMENT WITH MEBENDAZOLE OR PRAZIQUANTEL. DETAILED MEASUREMENTS WERE MADE ON 10 CYSTS IN EACH ORGAN

Treatment	Number of Lambs	Liver		Lung	
		Ext. Diam.	Int. Diam.	Ext. Diam.	Int. Diam.
Control	8	4.6 (1.4)†	3.2 (1.6)	7.9 (3.4)	6.6 (3.4)
Mebendazole for 14 days	8	3.6 (0.7)	1.8 (0.7) *	4.0 (0.8) *	1.8 (1.2) **
Mebendazole once intraperitoneal	7	4.6 (0.4)	3.2 (0.7)	6.0 (1.2)	4.4 (1.5)
Praziquantel once subcutaneous	4.5 (0.8)	3.3 (1.0)	6.7 (2.6)	5.4 (2.7)	

† = Number in brackets are standard deviation of mean between lambs.
* = $P<0.05$, ** = $P<0.01$ that means differs from that of controls.

TABLE IV: THE EFFECT OF MEBENDAZOLE OR PRAZIQUANTEL ON EIGHT-WEEK OLD *T. OVIS* CYSTS IN LAMBS INFECTED WHEN FIVE MONTHS OLD

Treatment	lamb number	number of live cysts	number of dead cysts	percentage of live cysts remaining
control	1	400	16	96
	2	476	20	95
	3	856	131	86
	4	108	9	92
	5	208	12	84
Mebendazole	1	0	486	0
50 mg/kg	2	10	432	2
orally each	3	0	745	0
day for	4	154	145	*52
14 days	5	6	727	1
Mebendazole	1	441	285	60
50 mg/kg	2	183	58	75
injected	3	279	193	59
intraperitoneally	4	144	103	58
	5	177	3	98
Praziquantel	1	0	336	0
50 mg/kg	2	0	538	0
injected	3	544	4	*99
subcutaneously	4	0	961	0
	5	0	395	0

* These cysts were apparently alive, but were not infective to dogs.

TABLE V: THE ESTIMATED SURVIVAL PROBABILITIES OF *T. HYDATIGENA* CYSTS IN LAMBS TREATED WITH SUBCUTANEOUS INJECTIONS OF PRAZIQUANTEL OR INTRAPERITONEAL INJECTIONS OF MEBENDAZOLE AT 50 mg/kg

Number of cysts to be treated	Estimated percentage survival following treatment
20	2
50	4
100	11
150	29
200	56
250	80
300	93
350	98
400	99

praziquantel did not differ significantly, but were different from that of the 14-day oral mebendazole treatment ($P<0.05$). Death of cysts was evidenced by a range of conditions, varying from a thick capsule around an immobile cysticercus with an evaginated scolex in a yellowish fluid, to a small hard nodule of 0.5-1.0 cm diameter containing no fluid and barely recognizable remnants of cestode tissue. Histological examination, compared with relatively transparent cysts from control animals, showed that the tegumental nuclei of affected cysts were degenerate, and that the calcareous corpuscles of the scolex region stained intensely with haematoxylin and eosin.

From Fig. 1 it is apparent that within each group, a range in numbers of cysticerci infesting individual sheep existed (10-410 cysts). The lethal effects of both the injected drugs were apparently decreased if the number of cysts in the animal exceeded 100-150 cysts. A regression model fitted to the pooled subcutaneous praziquantel and intraperitoneal mebendazole treatments fitted the data well ($r^2 = 0.41$, $F = 18.5$ on 1, 26 d.f. $P<0.001$) and gave the estimated survival probabilities shown in Table V.

E. granulosus cysts: Sheep harbouring all three species of larval cestodes, when examined 6 weeks after anthelmintic treatment, showed no differences in the numbers of cysts between groups. Except for the group treated orally with mebendazole for 14 days, the appearance of cysts was also similar. In this group the cysts appeared more dense macroscopically, and many did not contain fluid when sliced with a scalpel. Histological examination of these cysts compared with cysts from other groups revealed that some cysts had been killed, and most others showed a thickened host reaction around the cyst and a smaller inner cavity. Host cells were also closer to the parasite tegument than in healthy cysts.

When *E. granulosus* cysts were examined 5 months after anthelmintic treatment, only those cysts in animals treated for 14 days with mebendazole were obviously affected (Table III). Granulomata were smaller, and internal cavities of the cysts were either significantly smaller than the controls or were non-existent. Histological examination of these cysts showed that although many were dead, a few cysts appeared relatively normal. There were no signficant differences in the numbers of granulomata observed between groups.

T. ovis cysts: As seen in Table II most *T. ovis* cysts had died of natural causes before autopsy and had apparently begun to be resolved when examined 5 months after treatment, because fewer cysts were found than in animals examined 6 weeks after treatment. An estimate of drug action on this parasite species was therefore not possible, and a second experiment was carried out, making sure that times from infection to treatment and from treatment to autopsy were kept to a minimum.

In the second experiment (Table IV) *T. ovis* larvae was found to be susceptible to both praziquantel and mebendazole. One of the five sheep in the groups given mebendazole orally, and one sheep injected with praziquantel, still contained apparently viable cysts. The diaphragm of each of these two sheep was fed to respective dogs, and the diaphragms from 2 infected control sheep were fed to two other dogs. All dogs were from the same litter. At autopsy 2 weeks later, dogs fed cysts from untreated lambs each contained approximately 30 small *T. ovis* worms, while those fed cysts from treated lambs contained no worms. Histological examination of cysts that appeared still viable, but which had been treated with anthelmintic, revealed degeneration of tegumental nuclei and enhanced staining of calcareous corpuscles. Scoleces, however, were not evaginated as they were with *T. hydatigena* cysts, and did not evaginate until a thick capsule formed around the cyst. Stages of cyst degeneration ranged from a thickened capsule, evaginated scolex and decreased cyst fluid to a pronounced host reaction around the cyst, caseation of cyst contents and degeneration of cestode tissue. Although intraperitoneal injection of mebendazole significantly reduced the percentage of surviving cysts ($P<0.05$), the drug remained in the peritoneal cavity of all sheep, leading to the formation of abdominal adhesions.

DISCUSSION

Mebendazole is insoluble in water[19], and only slightly soluble in most organic solvents and thus is likely to dissolve only slowly in body fluids. In experiments with mice[10] 2-4 weeks were required for the subcutaneous drug depot to disappear, and with subcutaneous injections into rabbits, up to 15 weeks were required for the depot to be solubilized. In rabbits, however, almost all of the intraperitoneal injection had disappeared after 5 weeks. It therefore seemed likely that a single subcutaneous or intraperitoneal injection into sheep would provide a depot of drug that could be mobilized over some weeks, providing a continuous level of circulating anthelmintic in the body. Present results showed that these procedures were not satisfactory for sheep. Subcutaneous depots were mobilized too slowly to be effective against *T. hydatigena* cysts, and intraperitoneal injections, although being partially effective against *T. hydatigena* and *T. ovis* cysts, suffered from 3 disadvantages; they did not affect *E. granulosus* cysts; they caused extensive adhesions of the viscera; and they remained in the peritoneal cavity for very long periods. The oral administration of mebendazole has been shown to be the most effective method. The regime chosen, of 50 mg/kg for 14 days, killed virtually all *T. hydatigena* and *T. ovis* cysts. Further research is required to establish the most effective and the most practicable anthelmintic regime for sheep. Orally administered mebendazole is well tolerated by mice (M.L.D.50 = 4900 mg/kg[13]) and a single dose of a high concentration of this drug may prove of value for sheep.

Praziquantel is more soluble in water than is mebendazole, depots of the drug disappearing from the subcutaneous site within 2-3 weeks, leaving initially a reddish area which had disappeared by 6 weeks. Injections of praziquantel, at 50 mg/kg, were very effective against *T. hydatigena* and *T. ovis* cysts, and this may be the drug of choice, and the best method of application, for the control of these particular parasites in sheep. Unfortunately, praziquantel has no apparent effect on *E. granulosus* cysts. Presumably mebendazole and praziquantel act on different biochemical pathways in the parasite. Mebendazole has been shown to affect microtubules in the tegument of cestode larvae[2][12] while praziquantel paralyses *T. hydatigena* and *T. ovis* cysts *in vitro* within seconds of application (Heath, unpublished observations). The possibility exists that the two drugs may act synergistically against *T. hydatigena* and *T. ovis* cysts, and this is being investigated. Krotov[13] has already shown that mebendazole and levamisole act synergistically on the cysts of *E. multilocularis*. This synergism should also be investigated for *E. granulosus*.

The relationsip between number of *T. hydatigena* cysts and the predicted survival following a single injection of 50 mg/kg of mebendazole or praziquantel, indicates that the useful level of praziquantel for injection should not be less than 50 mg/kg. Mebendazole is accumulated in *Trichinella spiralis* larvae in concentrations higher than surrounding body fluid[7]. A similar situation could apply with larval cestodes. If a particular threshold concentration of drug is required for toxicity, the larger the biomass of parasites, the less drug there is available for each parasite. This seems to have been the case in the present experiments, both with injected praziquantel and injected mebendazole. Three or four hundred *T. hydatigena* cysts could occupy a volume of 1-2 litres. However, the drugs were effective with *T. ovis* cysts because 1000 of these cysts only occupy a volume of approximately 10 ml.

Praziquantel, injected at 50 mg/kg, now requires field testing to determine its usefulness in controlling infections of *T. hydatigena* and *T. ovis* in sheep. A more practicable method of administering mebendazole also needs to be investigated. Although the use of a slow-release capsule given orally is now possible, further development is required. Perhaps an initial high concentration of drug may prove as effective as low concentrations given over an extended period.

From the present experiments, and those carried out previously in laboratory animals[11] and in pigs[18], at least one repeat application of the oral drug regime is required for a complete kill of *E. granulosus* cysts. Further research is required with mebendazole to determine the best method of killing *E. granulosus* cysts.

Criteria for infectivity of *T. ovis* cysts following anthelmintic treatment, and similarly for *T. hydatigena* and *E. granulosus* cysts[11] may require reassessment. Morphologically undamaged *T. ovis* cysts, that attracted little host reaction, were nevertheless non-infective to dogs, and it is possible that *T. hydatigena* cysts, apparently surviving after drug treatment, were also non-infective. Intensive histological scrutiny has not revealed parameters that could be used to differentiate these apparently normal but uninfective cysts from controls. Further study is required to develop bilogical criteria for infectivity that will correlate well with the fate of ingested cysts in dogs.

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