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Significance of particle size of mebendazole in the treatment of tapeworm infections

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Taenia hydatigena and *Echinococcus granulosus* in dogs have been used as a model to evaluate the response of these parasites to increasing doses of mebendazole in different dose forms (powder, micronized powder and tablets of micronized powder). Overall the micronized powder proved to be the most active, the tablets less so and the normal powder least active. Statistical confirmation was obtained that the use of this drug in different dose forms changed the rate of the response, suggesting that in the treatment of human hydatid disease caused by *Echinococcus* spp and cysticercosis caused by *Taenia solium*, the dosage form may be a vital factor in the drug's efficacy.

Taenia solium cysticercosis and *Echinococcus* spp cause severe lesions in man. Until recently surgery was the only relief, but in many cases the lesions are inoperable and rapid deterioration in health is followed by early death. During the past few years, research has been undertaken on mebendazole, which has shown some promise against adult and larval cestodes in man and animals, but the reports on its efficacy have varied widely and many reasons have been given for this variability (Gemmell & Johnstone 1981; World Health Organization 1981; Schantz et al 1982). The drug has been administered to patients as tablets and no account has been taken of particle size. It has been suggested that there may be a loss of activity associated with the agglomeration of particles during the manufacture of tablets (Gemmell & Johnstone 1981). Continuation of trials with tablets alone may, therefore, result in continuing variable results in human medicine. This could cause the rejection of this promising drug for treatment of hydatid disease and cysticercosis. The possibility that particle size may determine efficacy has been examined in a trial involving dogs experimentally infected with *Taenia hydatigena* and *Echinococcus granulosus*.

Materials and methods

Two commercial micronized formulations of mebendazole (Telmintic powder and Telmin tablets) were studied for efficacy against *T. hydatigena* and *E. granulosus*. The nominal particle size was of the order of 86% less than 20 μm and 55% less than 10 μm. A third preparation, non-micronized powder (particle size 40% less than 21 μm and 18% less than 10 μm) was also tested against *T. hydatigena*. Dogs of mixed age but of fairly homogenous breed were infected with 3 scolices of *T. hydatigena* or 0·25 ml of protoscolices of *E. granulosus*. A simple treatment with one of the three forms of mebendazole was given on the 28th day after infection. The powders were sprinkled onto minced mutton and the tablets were inserted into it. In order to enable counts of the tapeworms to be made, autopsy was carried out 35 days after infection following an overdose of barbiturate.

The binomial proportions of dogs free of parasites after dosing were analysed using the probit link function and binomial errors in a generalized linear model (Nelder & Wedderburn 1972). Likelihood ratio tests were used to assess the relative importance of the dose levels and dose forms.

Results and discussion

Results are summarized in Table 1. Clearly, overall, the micronized powder was more active against *T. hydatigena* than the tablets or the non-micronized powder. The micronized powder was also more active overall than the tablets against *E. granulosus*, but higher doses were required to eliminate all worms. For both parasites linear models with different constant terms and different slopes were required to fit the data adequately. The predicting equations are given in Table 1. There is, therefore, clear evidence that the tablets prepared from micronized powder had activity different from the micronized powder itself.

The importance of particle size in the effectiveness of some drugs is well documented (Pritchard 1978), as is also the change in physical properties of powders when they are compressed into tablets (Schild 1980). It is clear from this study that the effectiveness of mebendazole against the adult form of *T. hydatigena* and *E. granulosus*, is affected by this phenomenon. There is evidence that the therapeutic effect of mebendazole in the treatment of porcine cysticercosis caused by *T. solium* is also influenced by particle size (Wang et al 1981). Those authors reported that the efficacy was negligible where particles exceeded 5 μm diameter.

The use of tablets in the treatment of human hydatidosis and cysticercosis may also result in a loss of bioavailability of small particles and the exclusion of the large particles by these larval forms, thereby accounting for the variable results reported in the literature.

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Table 1. The effect of micronized and non-micronized mebendazole powder on *Taenia hydatigena* and *Echinococcus granulosus* in dogs.

		Dose mg kg^{-1}					
		2·5	5·0	10·0	20·0	40·0	80·0
T. hydatigena							
Telmintic powder	Proportion of dogs with worms	3/10	1/10	0/10	0/10	0/10	Na
	Number of worms remaining	2, 2, 1	3	—	—	—	—
(Response curve −0·78525 + 1·38064 $\log_e$ dose)							
Telmin tablets	Proportion of dogs with worms	7/10	6/10	3/10	2/10	0/10	Na
	Number of worms remaining	3, 3, 2, 2, 2, 2, 1	3, 2, 1, 1, 1, 1	2, 2, 1	3, 1	—	—
(Response curve −1·47408 + 0·85532 $\log_e$ dose)							
Non-micronized mebendazole powder	Proportion of dogs with worms	6/10	3/10	6/10	2/10	3/10	Na
	Number of worms remaining	3, 2, 1, 1, 1, 1	3, 3, 1	2, 2, 1, 1, 1, 1	2, 1	2, 2, 1	—
(Response curve −0·35187 + −0·26653 $\log_e$ dose)							
E. granulosus							
Telmintic powder	Proportion of dogs with worms	—	6/10	4/10	1/10	0/10	0/10
	Number of worms remaining	—	14500, 12800, 171, 49, 4, 4	14200, 1410, 18, 4	68	—	—
(Response curve −0·64299 + 0·40446 $\log_e$ dose)							
Telmin tablets	Proportion of dogs with worms	—	5/10	3/10	3/10	4/10	0/10
	Number of worms remaining	—	3040, 1760, 1203, 225, 2	7775, 216, 14	1482, 56, 3	946, 25, 9, 2	—
(Response curve −2·35918 + 1·2235 $\log_e$ dose)							

Na = Not attempted.
Worms recovered from untreated controls:
Controls for *T. hydatigena*: 3, 3, 3, 3, 3, 2, 2, 2, 1, 1.
Controls for *E. granulosus*: 36350, 35350, 26700, 23200, 22300, 12550, 11480, 10967, 10733, 10267, 8672, 6260, 5183, 4520, 3300, 122, 29, 0, 0.

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