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Efficacy of Emodepside plus Praziquantel Tablets (Profender® Tablets for Dogs) against Mature and Immature Cestode Infections in Dogs

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Abstract

The efficacy of a novel flavoured tablet formulation of emodepside plus praziquantel (Profender® tablets for dogs) against intestinal cestodes was investigated in four randomised, blinded placebo-controlled dose confirmation studies in dogs experimentally infected with *Echinococcus granulosus* or *E. multilocularis* and in dogs naturally infected with *Dipylidium caninum* or *Taenia* spp. The tablets were used at the minimum recommended dose of 1 mg emodepside and 5 mg praziquantel per kg body weight. The studies demonstrated 100% efficacy against mature and immature *E. granulosus* and *E. multilocularis* and mature *Taenia* spp. and *D. caninum*. Additionally, one of the studies demonstrated non-interference of emodepside with the efficacy of praziquantel against *D. caninum*. No side effects of the treatment were observed. It is concluded that emodepside plus praziquantel tablets are safe and effective against mature and immature stages of *E. granulosus* and *E. multilocularis* and mature stages of *Taenia* spp. and *D. caninum*.

Introduction

Praziquantel has been in use as a reliable compound against cestode infections in dogs for a long time and was already described as an effective cestocidal drug by Thomas and Andrews in 1977. The efficacy of praziquantel against cestodes in dogs especially against *Echinococcus multilocularis* and *E. granulosus* has been demonstrated by many authors in the past (e.g., Dey-Hazra 1976; Rommel et al. 1976; Gyul'gyazli 1977; Sakamoto 1977; Kobulej and Varga 1978; Gemmel et al. 1980).

Both *E. granulosus* and *E. multilocularis* are zoonotic agents of major public health concern. *E. multilocularis* is widespread in rural and urban foxes of central Europe (Deplazes et al. 2004; Romig et al. 2006). Furthermore, dogs are susceptible definitive hosts of *E. multilocularis* with a high parasite egg reproduction (Kapel et al. 2006). Naturally infected dogs have been found in several epidemiological investigations (Deplazes et al. 2004; Dyachenko et al. 2008). The prepatent period in the definitive host after ingestion of an intermediate host (usually small rodents) is approximately 26–28 days (described in Eckert et al. 2008). Species of the *E. granulosus* complex (*E. granulosus* sensu stricto, *E. equinus*, *E. ortleppi*, *E. canadensis*) are less common in central Europe (Romig et al. 2006), however, these species are distributed worldwide with high variations in regional prevalences. Dogs represent the major definitive host for species of the *E. granulosus* complex and domestic animals such as sheep, cattle, pigs and horses serve as important intermediate hosts. The prepatent period in dogs varies between species but is reported to be in a range of 34–58 days (described in Eckert et al. 2008). *Dipylidium caninum* is the most common tapeworm in the dog in central Europe and has fleas and lice as intermediate hosts (described in Eckert et al. 2008). The parasite has only minor pathogenic and zoonotic significance. However, dogs can get frequently infected with this parasite, which is unpleasant for the dog, e.g., by causing anal pruritus. Also the presence of tapeworm proglottids in the faeces is repulsive to the dog owner.

Several *Taenia* spp. with a variety of intermediate hosts (rodents, ruminants) occur in dogs in Europe with very variable regional prevalences (described in Eckert et al. 2008). Intestinal *Taenia* infection is harmless in dogs, but can cause severe and occasionally lethal infections in their intermediate hosts.

Emodepside plus praziquantel tablets (Profender® tablets for dogs) are a new anthelmintic product indicated for dogs suffering from, or at risk from, mixed nematode and cestode infections, i.e., mature and immature *Toxocara canis*, *Toxascaris leonina*, *Ancylostoma caninum*, *Uncinaria stenocephala*, *Trichuris vulpis*, *Echinococcus granulosus*, *Echinococcus multilocularis* and mature *Dipylidium caninum* and *Taenia* spp. The efficacy has been confirmed in a series of laboratory dose confirmation studies and a multicentre field study (Altreuther et al. 2009a,b; Schimmel et al. 2009a,b).

This paper reports the findings of four laboratory studies (no. 1–4) that were conducted to investigate the efficacy of emodepside plus praziquantel tablets against mature and immature stages of *E. granulosus* and *E. multilocularis* (no. 1 and 2), and mature stages of *Taenia* spp. (no. 3) and *D. caninum* (no. 4) in dogs using the established standard dose of 5 mg praziquantel per kg body weight.

Materials and methods

The investigations were performed as placebo-controlled, blinded and randomised studies, conducted in accordance with the VICH guideline 9 "Good Clinical Practice" (July 2000), and followed the recommendations given in the VICH guidelines 7 "Efficacy requirements for anthelmintics: general requirements" (December 2000) and 19 "Efficacy of anthelmintics: specific recommendations for canines" (July 2001) and the WAAVP guideline for evaluating the efficacy of anthelmintics for dogs and cats (Jacobs et al. 1994).

The four studies were conducted as dose confirmation studies. Additionally, non-interference of emodepside and praziquantel with regard to the efficacy against *D. caninum* was investigated in study no. 4.

The study design is summarised in Table 1.

Study animals

The dogs used in the studies were either purpose bred dogs or animals acquired by the CRO in compliance with local regulations. They were identified by microchip, ear tattoo or numbered collar tag. In both *Echinococcus* studies (no. 1 and 2), the dogs were

housed in groups, but were kept single for 3 to 4 hours post treatment on the treatment days to enable individual clinical assessments. In studies no. 3 and 4, the dogs were individually housed in cages for the whole study duration. The dogs were fed with commercial dry dog food once daily and water was available *ad libitum*. All dogs were acclimatised for at least 7 days prior to the start of the study.

General requirements for study inclusion were good health and no recent anthelmintic use that could interfere with the study. Additionally, a positive diagnosis of infection with *Taenia* spp. or *D. caninum* based on at least two faecal examinations was required in studies no. 3 and 4.

During acclimatisation, the dogs of study no. 4 were treated with a prophylactic flea treatment containing imidacloprid (Advantage®, Bayer Animal Health) to prevent post treatment reinfection with *D. caninum*.

Clinical observations

The dogs were physically examined at least once during acclimatisation and once before treatment. Additionally, all dogs were observed for their general health at least once daily. On the day of treatment, clinical assessments with the aim to detect adverse events were conducted once before treatment and approximately 0.5, 1, 2, 3, 4 and 8 hours after treatment. The assessments were continued twice daily for two days after treatment.

Infection

In studies no. 1 and 2, protoscoleces of *E. granulosus* or *E. multilocularis* were mixed with small amounts of wet cat food and were fed individually to the dogs. In study no. 1, protoscoleces originated from hydatic cysts of slaughtered sheep in Kyrgyzstan (protoscoleces were transported in isolated cyst fluid or within the cysts and maintained at +4 °C for up to one week until use). *E. granulosus* sensu stricto (or former sheep strain) was confirmed by PCR (Stefanic et al. 2004). In study no. 2, the *E. multilocularis* originated from 2 dogs from Switzerland and had been passaged in Mongolian gerbils (*Meriones unguiculatus*) several times. *E. multilocularis* protoscoleces were isolated from metacestodes as described (Kapel et al. 2006) immediately after killing of the infected gerbils and kept at +4 °C around 3 hours until fed to the dogs. The other two studies (no. 3 and 4) were conducted with naturally infected dogs from the Republic of South Africa.

Treatment

Dogs of both sexes were randomly assigned to either treatment or control groups. In all studies, the dogs were treated once with emodepside plus praziquantel tablets or placebo tablets.

In the *E. granulosus* and *E. multilocularis* studies (no. 1 and 2), the treatment after experimental infection was timed so that the first group was treated when the parasites were immature. The second group was treated when the parasites were mature but prior to patency (see Table 1). This design was chosen to terminate the study before *Echinococcus* eggs were excreted and no high containment measures were required. For this reason, the recommendation of VICH GL 19 regarding the treatment time for evaluation of efficacy against adult stages of *E. granulosus* (> 28 days post infection) and the time for necropsy (10 to 14 days post treatment) were not followed.

In all studies, the dosage of emodepside and praziquantel was 1 mg emodepside and 5 mg praziquantel per kg body weight. In study no. 4 which was conducted as a non-interference study, one group received tablets containing only emodepside at a dose of 1 mg emodepside per kg body weight and another group received tablets containing only praziquantel at a dose of 5 mg praziquantel per kg body weight in addition to the control group and the group treated with emodepside plus praziquantel tablets. In all studies, the doses were based on the body weights of the day before treatment. Excess tablet substance was filed off until the tablet corresponded to the target weight for the individual dog. The emodepside plus praziquantel tablets, tablets containing either emodepside or praziquantel and the placebo tablets were administered orally by

forced dosing over the back of the tongue. Care was taken to ensure that all animals swallowed the full amount of the treatment without loss of product. The dogs were observed after dosing to determine whether any tablet matter was regurgitated.

Faecal examination

Animals designated for experimental infection with *E. granulosus* and *E. multilocularis* (study no. 1 and 2) were examined for the presence of cestode or nematode eggs in their faeces prior to infection using a sedimentation/flotation technique (Eckert et al. 2008). In both studies, the parasitological status was negative. For the diagnosis of the natural cestode infections in studies no. 3 and 4, faeces were examined for distinctive proglottids using sieving and microscopic evaluation techniques. The inclusion of eggs in uterine capsules and/or the presence of two sets of genital organs in each proglottid served as the diagnostic feature for *D. caninum*.

Necropsy

Four to twenty-one days post treatment the dogs were euthanised and subsequently necropsied (Table 1).

In studies no. 1 and 2, the small intestine was removed, opened longitudinally and divided into two pieces. These pieces were incubated separately in warm (approx. 37 °C) phosphate-buffered saline for 20–60 minutes to release most of the active worms into the fluid without contamination with mucosa. After removal of the pieces of intestine, worms were concentrated by sedimentation for approximately 10 minutes ("clean fraction"). The supernatant was

Table 1 Study design of controlled studies on the efficacy of emodepside (E) plus praziquantel (P) tablets against cestode infections (p.i.: post infection)

Study no.	Parasite species	Breeds	Age of dogs	Body weight (at day before treatment)	No. of dogs (EP group/ control group		Infection	Origin of natural infection/ isolate (age[a])	Treatment day	Necropsy day
1	*E. granulosus* (sensu stricto)	Beagle, crossbreeds[b]	Adult	8.5–16.1 kg	8 8	/8	Experimental ~ 19,300 protoscoleces	Kyrgyzstan, naturally infected sheep (≤1 week)	9 p.i. 23 p.i.	29/30 p.i.
2	*E. multilocularis*	Crossbreeds[b]	Adult	9.8–17.6 kg	8 8	/8	Experimental ~ 50,000 protoscoleces	Switzerland, naturally infected dog, passaged in *Meriones unguiculatus*[c] (1.5 and 3 years)	11 p.i. 21 p.i.	25/26 p.i.
3	*Taenia* spp.	Crossbreeds	Adult	3.7–18.9 kg	8	/8	Natural	Rep. of South Africa	0	10
4[d]	*D. caninum*	Crossbreeds	Adult	4.4–22.1 kg	8 (EP) 8 (E) 8 (P)	/6	Natural	Rep. of South Africa	0	10

[a] time since original isolation
[b] small swiss hound x Beagle
[c] mongolian gerbil
[d] study was conducted as a non-interference study including one group treated with emodepside only (E) and one group treated with praziquantel only (P)

used to wash the intestinal mucosa (supernatant and the pieces of intestine were placed in a bottle which was vigorously shaken) and then the mucosa was stripped. One washing step and subsequent sedimentation were performed for this fraction ("mucosa fraction"). For each fraction it was decided whether an aliquot or the full fraction would be investigated for worms. If none or only few worms could be macroscopically seen, the complete fraction was screened. If larger numbers of worms were seen at least 3 aliquots of at least 1/50 ("clean fractions") or 2/50 ("mucosa fraction") were taken and scoleces were counted. If the volume of the mucosa fraction could not be adjusted to less than 150 ml, an aliquot of 50 ml was taken and counted. The total worm number per fraction was calculated by multiplying the mean of the three counts (not rounded) with the volume of the fraction.

In studies no. 3 and 4, the digestive tract from the stomach to rectum was removed. The intestinal content and the results of several mucosal strippings of the small intestine were washed over sieves with apertures of 150 µm. The same procedures were applied to the large intestine using sieves with apertures of 300 µm. All samples were analysed for cestode scoleces identified to genus and species as far as possible.

Species determination of *Taenia* specimens

For species determination of *Taenia* specimens isolated at necropsy in study no. 3, the anterior end of the rostellum was sliced off and mounted in lactophenol (clearing agent) on a cavity slide with a cover slip. Five large and five small rostellar hooks were measured in each specimen and a mean length was calculated for each rostellum. Values were compared to the length ranges of hooks indicated for *T. hydatigena*, *T. multiceps* and *T. ovis* by Verster (1969).

Efficacy determination and statistical analysis

In all studies, adequacy of infection in the control group was assessed according to the methods suggested in VICH guidelines 7 and 19. A minimum of 6 control animals with at least 1 scolex recovered for *Taenia* spp. and *D. caninum* or at least 5 scoleces for *E. granulosus* and *E. multilocularis* were set as a requirement. Additionally, the intensity of infection was considered adequate if the lower 95% confidence limit was greater than 10% of the central tendency (geometric mean if all worm counts in the control group > 0, or median if one or more worm counts in the control group = 0).

Percent efficacy for each treatment was calculated according to VICH guideline 7 recommendations and the WAAVP guideline for evaluating the efficacy of anthelmintics for dogs and cats (Jacobs et al. 1994) as follows:

$$\% \text{ Effectiveness (reduction)} = \frac{(N1 - N2)}{N1 \times 100}$$

N1: geometric mean scolex count for the control group
N2: geometric mean scolex count for the treatment group

Geometric means were calculated following transformation using a logarithmic method (averaging the transformed values, and converting the average using antilog to represent a geometric mean). Because neither the actual scolex counts nor the logarithmically transformed counts were distributed normally, the non-parametric Wilcoxon rank sum test (two-tailed, using $\alpha = 0.05$) was used to test for both gender and treatment group (emodepside plus praziquantel tablet or monoformulation vs. placebo) effects. The analyses were performed using SAS software (SAS® Institute, Cary, NC, USA).

Results

None of the dogs from the four studies showed signs of adverse reactions after treatment until necropsy. The requirements for the adequacy of infection in the control group were fulfilled in all studies.

Table 2 Results of controlled studies on the efficacy of emodepside (E) plus praziquantel (P) tablets against mature and immature *E. granulosus* and *E. multilocularis* (p.i.: post infection)

Study no.	Parasite species	Treatment day (target stage)	No. of dogs in control group with ≥ 5 worms/ total no. of dogs in control group	Worms per group at necropsy (EP/control)			Efficacy	p-value
				Total no.	Range	Geometric mean		
1	*E. granulosus* (sensu stricto)	9 p.i. (immature)	8/8	0/41,511	0/ 225–12,868	0/3,097	100 %	0.0030
		23 p.i. (mature)		0/41,511	0/ 225–12,868	0/3,097	100 %	0.0030
2	*E. multilocularis*	11 p.i. (immature)	8/8	1/ 128,669	0–1/ 5,879–25,961	0.1/ 14,638	100 %	0.0035
		21 p.i. (mature)		0/ 128,669	0/ 5,879–25,961	0/14,638	100 %	0.0030

Table 3 Results of controlled studies on the efficacy of emodepside (E) plus praziquantel (P) tablets against natural infection with *D. caninum* and *Taenia* spp.

Study no.	Parasite species	Target stage	No. of dogs in control group with ≥ 1 worms/ total no. of dogs in control group	Worms per group at necropsy			Efficacy	p-value
				Total no.	Range	Geometric mean		
3	*Taenia* spp.	Mature	8/8	EP/control 0/24	EP/control 0/1–8	EP/control 0/2.3	100 %	0.0028
4[a]	*D. caninum*	Mature	6/6	EP/control 0/323	EP/control 0/1–227	EP/control 0/21.7	100 %	0.0051
				E/control 302/323	E/control 2–71/1–227	E/control 22.1/21.7	No efficacy	0.6588
				P/control 0/323	P/control 0/1–227	P/control 0/21.7	100 %	0.0051

[a] study was conducted as a non-interference study including one group treated with emodepside only (E) and one group treated with praziquantel only (P)

Efficacy of emodepside plus praziquantel tablets against immature and mature stages of *E. granulosus* and *E. multilocularis* was 100 % (Table 2). Studies no. 3 and 4 demonstrated 100 % efficacy of emodepside plus praziquantel tablets against natural *Taenia* spp. and *D. caninum* infection (Table 3). All differences between treatment and control groups were statistically significant and no gender effect was found.

In study no. 3, the rostellar hook size for the majority of the specimens fell within or close to the size range published for *T. hydatigena* (Verster 1969). The remaining specimens may have been *T. ovis* or *T. multiceps*.

Regarding the evaluation of non-interference of emodepside with praziquantel in study no. 4 no efficacy against *D. caninum* was observed in dogs that had received emodepside tablets without praziquantel and there was no statistically significant difference between the worm burdens of these dogs and the control dogs ($p = 0.6588$). Tablets containing praziquantel without emodepside were 100 % efficacious and there was no statistically significant difference between the worm burdens of

dogs that had received this formulation and the dogs that had received emodepside plus praziquantel tablets (p=1.0000). The results are presented in detail in Table 2, 3.

Discussion

The studies presented in this paper demonstrated 100% efficacy of emodepside plus praziquantel tablets against mature and immature *E. granulosus* and *E. multilocularis*, and against mature *Taenia* spp. and *D. caninum*. Additionally, study no. 4 showed that emodepside does not interfere with the efficacy of praziquantel and that praziquantel is solely responsible for the efficacy against cestodes in this formulation. No side effects of the treatment were observed in the dogs in the four studies.

High efficacy against *E. multilocularis* and *E. granulosus* was not only demonstrated against mature stages but also against early stages, 9 to 11 days post infection, which can be regarded as very important considering the zoonotic potential of this parasite.

It is known that *Taenia* spp. are more sensitive to praziquantel than *D. caninum* or *Echinococcus* spp. and that a reliable efficacy can be expected already at lower doses than the standard dose of 5 mg praziquantel per kg body weight. However, one study (no. 3) was conducted to verify the efficacy of the new formulation against this genus. Comparing the literature on the efficacy of praziquantel against different *Taenia* spp., *T. hydatigena* can be suspected to be slightly less susceptible than other species like *T. ovis* or *T. pisiformis*. Oral doses of 1 mg praziquantel per kg body weight have been reported to be 100% effective against *T. ovis* (Gemmell et al. 1977) and *T. pisiformis* (Dey Hazra 1976), while this dose was described to have variable efficacy against *T. hydatigena* (Dey Hazra 1976). For this reason, the *Taenia* specimen in study no. 3 were further investigated with regard to their species and found to be predominantly *T. hydatigena* so that efficacy was verified using the potentially less susceptible *Taenia* species.

The data presented in this paper were confirmed by the results of a multicentre field study conducted in 33 veterinary practices in France, Germany, Portugal and Slovakia where 100% efficacy of emodepside plus praziquantel tablets was shown in 24 dogs naturally infected with *D. caninum*, 11 dogs naturally infected with taeniids and 6 dogs naturally infected with *Mesocestoides* spp. (Altreuther et al. 2009a).

It can be concluded that emodepside plus praziquantel tablets (Profender® tablets for dogs) are an effective and safe treatment against mature stages of *D. caninum* and *Taenia* spp. and mature and immature stages of *E. multilocularis* and *E. granulosus*.

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