Parasitol Res (2011) 109:S1–S8 DOI 10.1007/s00436-011-2397-1

Efficacy of Emodepside plus Toltrazuril (Procox® Oral Suspension for Dogs) against *Toxocara canis*, *Uncinaria stenocephala* and *Ancylostoma caninum* in Dogs

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Abstract

The efficacy of emodepside plus toltrazuril (Procox® oral suspension for dogs) against different species of gastrointestinal nematodes (*Toxocara canis*, *Ancylostoma caninum*, *Uncinaria stenocephala*) was evaluated in nine randomised, blinded and placebo-controlled laboratory studies in naturally or experimentally infected dogs. The product was used at the proposed minimum dose of 0.45 mg emodepside and 9 mg toltrazuril per kg body weight. Efficacy was calculated based on worm counts after necropsy.

Worm burdens in the control dogs ranged between 0 and 409 worms of the respective stage for *T. canis* and between 4 and 655 worms for hookworms. The studies demonstrated 100% efficacy of emodepside/toltrazuril suspension against mature adult, ≥94.7% efficacy against immature adult and 99.3% efficacy against the L4 larval stage of *T. canis*. The efficacy against mature adult *A. caninum* was ≥99.5% and the efficacy against mature adult *U. stenocephala* was 100%. All differences between treatment and control groups were statistically significant and no gender effect was found. It can be concluded that the emodepside/toltrazuril suspension represents a safe and highly effective product in dogs with nematode (*T. canis*, hookworms) infection.

Introduction

Nematodes in dogs are an important group of endoparasites in which *Toxocara canis* and hookworms are of special interest (Epe et al. 2004; Pullola et al. 2006). The prevalence described in studies performed in many parts of the world varies considerably. *Toxocara canis* is the most frequently encountered, with prevalence in Europe often ranging up to 32 % (Fok et al. 2001; Sager et al. 2006; Grandemange et al. 2007; Wright and Wolfe 2007; Nikolic et al. 2008). Ancylostomatidae, as the second most common nematodes, are found up to 13.1 % with an even higher prevalence rate of up to 32 % in stray, shelter and kennel dogs (Fok et al. 2001; Pullola et al. 2006; Grandemange et al. 2007; Martinez-Carrasco et al. 2007). Generally, it has to be considered that cited prevalence cannot be compared directly as the examined populations are quite different to each other (Schnieder et al. 2011). Additionally, Wolfe et al. (2001) found in foxes that the faecal flotation method underestimated the true prevalence of *T. canis* by 46.7 % and of *Uncinaria* species by 31 %, so the true prevalence in the dog populations studied may actually be much higher. Many publications on parasite prevalence present details on age groups, and generally, prevalence of *Toxocara canis* is considerably higher in puppies and young dogs compared to older dogs (Wright and Wolfe 2007; Fok et al. 2001; Pullola et al. 2006; Martinez-Carrasco et al. 2007; Ugbomoiko et al. 2008). This matches with prenatal transmission being the most important way of *T. canis* infection in dogs. Parenteral infections of puppies occur not only after the infection of the pregnant bitch but also through reactivation of somatic tissue larvae from earlier infections (Webster 1958; Koutz et al. 1966). The developmental cycle of *T. canis* is complex and can involve migration of larval stages through various organs including the lungs, liver and kidneys before reaching the small intestine where development to the adult stage is completed or enters a hypobiotic stage, e.g. in muscle tissue. The different pathways and times for development depend on multiple factors including the route of infection (oral or prenatal), infection dose, age and immune status of the dog so that prepatency can be as short as ~ 3 weeks after a prenatal infection and up to ~ 6 weeks after an oral infection (Parsons 1987). The lactogenic transmission is of lesser importance for the infection of dogs with *T. canis* (Burke and Roberson 1985a,b).

Infections with *Uncinaria stenocephala* mainly take place by the oral route, while infections with *Ancylostoma caninum* can be caused orally as well as percutaneously. The prepatent period has been reported to be ~ 2–3 weeks. However, the time taken to develop to maturity depends also on a variety of factors including host immunity and the route of infection (Bowman et al. 2010).

Emodepside/toltrazuril suspension is a new combination of two already known actives in veterinary medicine. Emodepside is a semi-synthetic derivate of PF1022A and belongs to the cyclic depsipeptides. Emodepside binds to a presynaptic latrophilin receptor which belongs to the group of the G-protein-coupled receptors (Willson et al. 2003; Harder et al. 2005). In addition, emodepside acts via a second target, a Ca^{++}-activated K^+ channel. This channel belongs to the large conductance calcium- and voltage-activated potassium channels, termed SLO-1, which generally are important regulators of cell excitability. The end effect of emodepside is flaccid paralysis and death of the nematode (Holden-Dye et al. 2007).

Toltrazuril has been used in veterinary medicine since the 1980s. It has broad-spectrum activity against species of various genera of coccidia (*Eimeria*, *Isospora*, *Toxoplasma*, *Sarcocystis* etc.) in a wide range of livestock and companion animals.

The combination of these two actives, emodepside and toltrazuril (Procox® suspension) is indicated for dogs, including puppies from 2 weeks of age and young dogs, when mixed parasitic infections caused by roundworms and coccidia of the following species are suspected or demonstrated: *Toxocara canis* (mature adult, immature adult, L4), *Uncinaria stenocephala* (mature adult), *Ancylostoma caninum* (mature adult), *Isospora ohioensis*-complex and *Isospora canis*.

Emodepside has already been proven to be effective against nematodes in dogs applied as emodepside plus praziquantel in a tablet formulation, Profender® tablets, Bayer Animal Health GmbH, Leverkusen, Germany (Altreuther et al. 2009a,b; Schimmel et al. 2009). The present paper focuses on the nematocidal efficacy of emodepside/toltrazuril suspension and nine controlled laboratory studies against mature and immature stages of *T. canis* and mature hookworms in naturally and experimentally infected dogs are described.

Materials and methods

The efficacy of emodepside/toltrazuril suspension (Procox®) against different species of gastrointestinal nematodes (*Toxocara canis*, *Ancylostoma caninum*, *Uncinaria stenocephala*) and developmental stages of *T. canis* was investigated in nine laboratory studies. The study designs are summarised in Tab. 1.

All studies were conducted in accordance with VICH guideline 9 "Good Clinical Practice" (July 2000) and followed the recommendations given in the VICH guidelines 7 "Efficacy requirements for anthelmintics: overall guidelines" (December 2000) and 19 "Efficacy of anthelmintics: specific recommendations for canines" (July 2001) as well as the WAAVP guideline for evaluating the efficacy of anthelmintics for dogs and cats (Jacobs et al. 1994).

Study animals

The dogs used in the studies were either purpose-bred individuals from different suppliers, animals owned by the contract research organisations (CRO) or animals obtained from commercial kennels according to the respective local regulations. In total 143 healthy Beagle or crossbred dogs (6 weeks to adult, 67 male, 76 females) weighing between 0.8 and 16.6 kg were enrolled. The dogs were either identified by ear tattoo, numbered collar tags or subcutaneously implanted microchip and were housed single or in groups. After randomisation, it was ensured that only dogs of the same group were housed together. At least on the day of treatment and the following two days, the dogs were housed individually. Commercial dog food was provided once or twice per day 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. Dogs included in the six studies that used experimental infections were required to be negative for nematodes before infection as examined by faecal egg counts during acclimation (no. 1, 3–6, 9). Dogs included in studies that investigated efficacy against patent infections (no. 1, 2, 6–9) were required to demonstrate at least 2 positive faecal egg counts before treatment.

Clinical observations

In all studies, dogs were physically examined at least once during acclimation and once before treatment. Additionally, all dogs were observed for their general health once daily except for treatment days and the two following days, when clinical assessments were conducted instead. On treatment days clinical assessments were conducted once pre treatment and ~ 0.5, 1, 2, 3, 4 and 8 hours post treatment. Clinical assessments were continued twice daily for the following two days.

Infection

Three studies (no. 2, 7, 8) were conducted with naturally infected dogs in the USA and the Republic of South Africa. In the other studies, dogs were orally infected with embryonated *T. canis* eggs or hookworm larvae. The origin of the isolates and doses used for infection are shown in Tab. 1.

Treatment

Dogs were randomised by sex and body weight and allocated to either treatment (71 dogs) or control (72 dogs) group and treated once with emodepside/toltrazuril or placebo suspension. In the six studies investigating efficacy against mature adult stages, animals were treated after patency had been

demonstrated. In the three studies investigating the efficacy against immature stages of *T. canis*, treatment was applied 21 days post infection (Tab. 1).
In all studies, the minimum therapeutic dose of 0.45 mg emodepside and 9 mg toltrazuril per kg body weight was administered based on the body weights taken either one or two days before treatment. The suspension was orally applied using a syringe and ensuring that the full dose was swallowed by the dog. The dogs were observed at dosing and ~ 30 minutes after dosing to determine any vomiting or regurgitation. All dogs were fed immediately after treatment to ensure conservative conditions as the c_{max} of emodepside in the suspension tends to be lower in fed dogs (unpublished data).

Faecal examination

Pre treatment faecal egg counts were conducted to monitor presence or absence of nematodes using modified McMaster or quantitative centrifugation methods. In two of the studies with natural infections (no. 2, 8) worms were collected daily post treatment from the faeces using sieving techniques as described below for necropsy.

Necropsy

Five to 7 days post treatment all dogs in these studies were euthanised and necropsied. At necropsy, the digestive tract from stomach to rectum was removed. The intestinal contents and the results of several mucosal strippings of the small and large intestines were washed over sieves with apertures of 50 µm to 250 µm.
In study 5 the small intestines were additionally soaked in 0.9 % saline at ~ 37 °C for 2–3 hours to encourage release and sedimentation of adherent larvae. After soaking the saline solution was passed through a 50 µm aperture sieve and the small intestines were stripped and washed again using the same sieve. All samples were analysed for

Tab. 1 Animal details and design of the nine studies

Parasite	Study no.	Breeds	Age of dogs at treatment (months)	No. of dogs (treated/ control)	Infection	Origin of isolate/ natural infection	Treatment (days post infection)	Necropsy (days post treatment)
T. canis	1	Beagle	4–5	7/8	Experimental (~ 300 eggs)	Germany	49	7
	2[a]	Cross-breeds	1.5–4	8/8	Natural	South Africa	–	7
	3	Beagle	3.5	8/8	Experimental (~ 300 eggs)	Germany	21	5
	4	Beagle	3.5	8/8	Experimental (~ 500 eggs)		21	5
	5	Beagle	3–3.5	8/8	Experimental (~ 300 eggs)	Ireland	21	5
A. caninum	6	Beagle	3.5–4	8/8	Experimental (~ 300 larvae)	Africa	23	7
A. caninum + *U. stenocephala*	7	Beagle, cross-breeds	3–4	8/8	Natural	USA	–	7
U. stenocephala	8[a]	Cross-breeds	> 4	8/8	Natural	South Africa	–	7
	9	Beagle	3.7	8/8	Experimental (~ 1,000 larvae)	Italy	22	7

[a] additional faecal worm counts post treatment to necropsy

mature and immature worms, and the recovered specimens were counted and differentiated according to genus, species and developmental stage.

Efficacy determination and statistical analysis

Adequacy of infection in the control group was assessed according to the methods suggested in VICH guidelines 7 and 19 that require a minimum of 6 control animals with at least 5 worms each. Additionally, the intensity of infection was considered adequate when 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:

% effectiveness (reduction) = (N1 – N2)/N1 x 100

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

Geometric means were calculated following transformation using a logarithmic method (averaging the transformed values and converting the average using anti-log to represent a geometric mean). Because neither the actual worm 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/toltrazuril suspension vs. placebo) effects. The analyses were performed using SAS software (SAS® Institute, Cary, NC, USA).

Tab. 2 Results of *T. canis* worm counts at necropsy per study and developmental stage

Developmental stage	Study no.	Treatment day (days post infection)	Control group: dogs (n) with ≥ 5 worms	No. of worms (treated/control)	Range of worms (treated/control)	Treated group: dogs (n) negative	Geometric mean of worms (treated/control)	Efficacy	p value
Mature adult	1	49	8	0/141	0/10–36	7 of 7	0/16.0	100 %	0.0047
	2	–	4[a]	0/85	0/0–6	8 of 8	0/7.5	100 %	0.0030
Immature adults	1[b]	49	1	0/15	0/0–6	7 of 7	0/1.4	n.c.	
	3[c]	21	5	3/71	0–2/0–33	6 of 8	0.3/5.0	94.7 %	0.0004
	4[c]	21	4	2/41	0–1/0–14	6 of 8	0.2/3.4		
	5	21	7	16/370	0–5/1–77	3 of 8	1.4/32.3	95.7 %	0.0136
L4 larvae	3	21	4	0/45	0/0–16	8 of 8	0/3.0	n.c.	
	4	21	6	1/493	0–1/1–409	7 of 8	0.1/12.8	99.3 %	0.0039
	5	21	8	6/509	0–5/16–101	6 of 8	0.4/52.6	99.3 %	0.0040

n.c.: not calculated, because of low infection in control group
[a] efficacy calculated despite < 6 adequately infected control dogs (see results)
[b] although this study was designed for efficacy evaluation against mature adults, a few immature adult worms were found in the control group
[c] data on immature adult *T. canis* of study 3 + 4 were combined because of inadequate infection of control groups

Tab. 3 Results of mature adult *A. caninum* and *U. stenocephala* worm counts at necropsy

Parasite	Study no.	Control group: dogs (n) with ≥ 5 worms	No. of worms (treated/control)	Range of worms (treated/control)	Treated group: dogs (n) negative	Geometric mean of worms (treated/control)	Efficacy	p value
A. caninum	6	8	1/458	0–1/46–79	7 of 8	0.1/56.3	99.8 %	0.0035
	7	8	39/1418	0–39/16–379	7 of 8	0.6/120.7	99.5 %	0.0044
U. stenocephala	7	7	0/462	0/4–174	8 of 8	0/36.5	100 %	0.0030
	8[a]	8	0/1448	0/57–468	8 of 8	0/140.9	100 %	0.0030
	9	8	1/4402	0–1/286–655	7 of 8	0.1/533.6	100 %	0.0035

[a] additional gastrointestinal nematodes found (see results section)

Results

The requirements for an adequate infection of the control group were fulfilled in all hookworm studies. In three of the *T. canis* studies efficacy was calculated even though the criterion for 6 control dogs with a minimum of 5 worms of the respective stage was not met. In study 2 only four control dogs were adequately infected with mature adult *T. canis* and two control dogs had four worms each. As also faecal worm counts were examined in this study it could be shown that six of the eight treated dogs had shed 6 to 36 *T. canis* worms within 2 days after treatment. Therefore the infection of the treated dogs was regarded as adequate for the study. Studies 3 and 4 were conducted at the same location under similar conditions and did not show significant differences between the worm burdens of the two control groups. Therefore, the data for the immature adult worms from studies 3 and 4 were pooled to fulfil the requirements for adequate infection.

Thus, for each investigated parasite stage of *T. canis,* efficacy was calculated from 2 data sets and a 100 % efficacy against mature adult, ≥ 94.7 % efficacy against immature adult and 99.3 % efficacy against the L4 larval stages was demonstrated (Tab. 2). The efficacy of the emodepside/toltrazuril suspension against mature adult *A. caninum* was ≥ 99.5 % and the efficacy against mature adult *U. stenocephala* was 100 % (Tab. 3). All differences between treatment and control groups in all studies were statistically significant and no gender effect was found.

Faecal worm counts conducted additionally in two studies (no. 2, 8) showed that *T. canis* and *U. stenocephala* were expelled within 2 days after treatment. In study 8 the treated dogs also expelled *A. caninum* (5 dogs), *T. canis* (2 dogs), *Toxascaris leonina* (2 dogs) and *Trichuris vulpis* (7 dogs). At necropsy no nematodes were found in these dogs except for one dog with three immature *T. leonina*. Two dogs (study 1, 4) vomited food within half an hour after treatment. No other clinical signs were observed that were regarded as potentially treatment related.

Discussion

All nine studies presented in this paper demonstrated efficacy against mature adults, immature adults and L4 larvae of *T. canis* and against mature adult hookworms. The treatments were well tolerated in all dogs. The vomiting of two dogs (study 1, 4) within half an hour after treatment may have been due to the fact that they had consumed their entire food ration within half an hour post treatment coupled with the excitement related to treatment procedures. The efficacy results demonstrated in these laboratory studies were confirmed in a multicentred

field study performed across Europe in one month to 11 years old dogs. An efficacy of 100 % against *T. canis* and 99.9 % against Ancylostomatidae based on faecal egg count reduction was demonstrated. In 90 % of the dogs a good acceptance was described (Altreuther et al. 2011). These results match the efficacy results described for the emodepside/praziquantel tablet (Profender® tablets for dogs) and confirm emodepside as an effective nematocidal active (Altreuther et al. 2009a,b; Schimmel et al. 2009).
The trans-mammary and prenatal transmission of *T. canis* and *A. caninum* in the bitch is the cause for special interest, attention and the necessity to take measures to protect especially puppies and young dogs from parasitic infections. Puppies can be severely infected by these intestinal worms before diagnosis is possible by faecal examination. Furthermore, *Isospora* spp. infections are very common, particularly in young dogs (Lappin 2010). Both nematodes and *Isospora* spp. share the same target organ and cause similar pathology and subsequent clinical signs such as diarrhoea. To decrease contamination of the environment and thus lower the risk of reinfection, a regular early started and reliable parasitic treatment is necessary. ESCCAP (2010) recommend for this reason to start an anthelmintic treatment when puppies are 2 weeks of age. The emodepside/toltrazuril suspension was proven to be safe for puppies from 2 weeks onwards (unpublished data) and is, therefore, suited as a reliable parasitic treatment starting at this early recommended time point if a co-infection with *Isospora* spp. is suspected or demonstrated.

Acknowledgements

The authors thank all technical personnel involved in the studies.

Compliance statement

All of the studies reported herein were performed in compliance with current, applicable, local laws and regulations.

Disclosure statement

A. Schimmel, I. Schroeder, G. Altreuther and K. J. Krieger were employed by Bayer Animal Health GmbH, Germany, and T. Settje, S. Charles and D. Hutchens were employed by Bayer HealthCare LLC, USA, during the conduct of these studies. S. Wolken, D. J. Kok, J. Ketzis and D. Young were employees of University of Veterinary Medicine Hannover, Germany, ClinVet International (Pty) Ltd., Charles River Laboratories, Ireland, and Young Veterinary Research Services, USA, respectively, and conducted the studies as CROs. All studies were sponsored by Bayer Animal Health GmbH.

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