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Short communication

Comparative effects of milbemycin oxime-based and febantel–pyrantel embonate-based anthelmintic tablets on *Toxocara canis* egg shedding in naturally infected pups

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Abstract

The effect of two treatment programmes on egg shedding in dogs naturally infected with *Toxocara canis*, one based on a milbemycin oxime–praziquantel–lufenuron combination (SENTINEL® Spectrum; Group 1) and the other based on a febantel–pyrantel embonate–praziquantel combination (DRONTAL® Plus; Group 2), was compared in a study involving 104 suckling pups from three different kennels. The animals in Group 1 were treated at a minimum milbemycin oxime dose of 0.5 mg/kg bw starting at 2 weeks of age and subsequently every 4 weeks until reaching 26 weeks of age. The animals in Group 2 were treated every 2 weeks from week 2 until week 12 of age and then once at week 26 at a minimum febantel and pyrantel embonate dose of 15.0 and 14.4 mg/kg bw, respectively. *Toxocara* egg counts were determined fortnightly starting at 2 weeks of age and continuing until 26 weeks of age for every pup. Any adverse drug event was recorded during the trial. Both treatment programmes significantly reduced the zoonotic *Toxocara* egg shedding and were well tolerated by the pups. The pups in Group 1 showed lower average faecal egg counts and were found more frequently shedding no eggs than the pups in Group 2.

Keywords: *Toxocara canis*; Dog; Pup; Milbemycin oxime; Febantel; Pyrantel embonate

1. Introduction

The efficacy against *Toxocara canis* of febantel and pyrantel salts, applied alone or in combination with other anthelmintics, has been widely investigated in adult dogs (e.g., Lindquist, 1975; Klein et al., 1978; Corwin et al., 1984; Hopkins, 1991; Greiner et al., 1992; Lloyd and Gemmell, 1992; Dryden and Ridley, 1999) but less so in naturally infected, unweaned pups (Jacobs, 1987; Christensson et al., 1991; Fisher et al., 1994) and not beyond 17 weeks of age. For milbemycin oxime all the investigations on its efficacy

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against *T. canis* in dogs published so far were carried out on adult or adolescent animals (Bowman et al., 1988, 2002; Reinemeyer et al., 1995). The present investigation was carried out to compare the efficacy of two combination products against *T. canis*, one based on milbemycin oxime (SENTINEL® Spectrum) and the other on febantel–pyrantel embonate (DRONTAL® Plus), administered to pups during their first 24 weeks of life following the specific treatment regime recommended by the manufacturer.

2. Materials and methods

A total of 104 suckling pups from 42 litters of three different kennel sites in the UK were included in the study. Twenty-nine pups were sourced from kennel A (Harriers), 19 from kennel B (Beagles) and the remaining 56 from kennel C (represented breeds: Labrador, Golden Retriever, Labrador cross Golden Retriever, black Labrador cross German shepherd and Flat Coated Retrievers cross Golden Labrador). The bitches had not been treated with any medicine for the 2 months preceding delivery of the pups nor whilst suckling. Only healthy pups of at least 2 weeks of age and 0.5 kg bodyweight of either sex and having passed a veterinary examination were included in the study. Allocation of the pups to Group 1 to be treated with a milbemycin-based combination tablet (SENTINEL® Spectrum Novartis Animal Health Inc., Switzerland) or to Group 2 to be treated with a febantel–pyrantel embonate combination tablet (DRONTAL® Plus, Bayer Ltd., Germany) was done by random. All pups were treated orally after food starting at 2 weeks of age following the instructions for use of the corresponding product. Those in Group 1 were treated every 4 weeks and those in Group 2 every 2 weeks until 12 weeks of age and thereafter once at 26 weeks of age. The applied dosing resulted in a minimum dose of 0.5 mg/kg bw milbemycin oxime for the pups in Group 1 and of 15.0 and 14.4 mg/kg bw febantel and pyrantel embonate, respectively, for the pups in Group 2. For both groups, the last treatment was administered when the pups were 26 weeks old. All pups were weighed on the day of the first treatment and thereafter every 2 weeks. They were housed with their mothers until weaning to solid food at 6 or 8 weeks of age. After weaning, the animals lived in the private home of the walker/carer with the exception of a few hunt dogs that remained at the kennel. The administration of any other anthelmintic drug was prohibited for the duration of the study. Adverse events occurring before of after weaning were recorded for each individual animal. Faeces from each pup were collected every 14 days starting 2 weeks after the first treatment. Faecal samples were examined quantitatively for *T. canis* eggs using a modified McMaster technique. The study was blinded by function. The persons preparing and administering the doses or otherwise knowing the group allocation (e.g., the witnesses of dose prepara-

Table 1
Mean (arithmetic) faecal egg counts (epg) determined for pups treated with milbemycin-based (Group 1) or with febantel–pyrantel embonate-based (Group 2) tablets

Day	Group	*N*	Percentage FEC > 0[a]	Mean (*a*)[b]	S.D.	*p*-Value[c]
14	1	47	10.6	2334.0	9335	0.0070*
	2	49	34.7	4919.0	10880	
28	1	45	11.1	1490.0	8299	0.1186
	2	48	22.9	1763.0	7629	
42	1	50	8.0	34.0	163	0.3129
	2	50	14.0	339.0	1508	
56	1	47	6.4	16.0	72	0.6444
	2	50	4.0	102.0	622	
70	1	48	6.3	8.3	39	0.3303
	2	48	2.1	21.9	152	
84	1	47	4.3	19.1	106	0.2832
	2	49	10.2	21.4	77	
98	1	42	11.9	56.0	249	0.5429
	2	49	16.3	50.0	146	
112	1	45	11.1	76.7	239	0.0530
	2	50	30.0	80.0	161	
126	1	47	14.9	14.9	45	0.3241
	2	49	20.4	83.7	213	
140	1	46	8.7	23.9	84	0.2711
	2	45	15.6	92.2	247	
154	1	46	6.5	30.4	160	0.2766
	2	45	13.3	55.6	193	
168	1	44	2.3	1.1	8	0.0473*
	2	44	13.6	71.6	337	

[a] Percentage of animals with positive faecal egg counts.
[b] Including negative faecal egg counts.
[c] Mann–Whitney *U*-test.
* Significant: $p < 0.05$.

tion and administration) were not involved in any observation used as end-points for the study, e.g., faecal egg counts (FEC).

Summary statistics including arithmetic mean, minimum, maximum, and median were determined for all continuous parameters. FEC observations for each treatment group were summarized and compared by Mann–Whitney *U* tests. Average AUC levels for the individual pups in both groups were calculated using the trapezoidal rule and divided by the individual length of the observation period, and these AUC[t] levels were compared for both groups (Mann–Whitney *U*-test, two-tailed). A non-inferiority analysis was also applied on log-transformed, non-zero average AUC[t] levels. The assumption of normal distribution was considered as satisfied for $p = 0.7366$ (Shapiro–Wilk test). The relative egg count proportion was calculated as the geometric mean of average AUC[t] Group 2 levels over the geometric mean of average AUC[t] Group 1 levels. The occurrence of adverse events in both groups was compared between pups with at least one adverse event and pups without any adverse event using a Fisher exact probability test. The level of significance tests was $a = 5\%$; all tests were performed two-sided.

3. Results

There was no statistical difference between the treatment groups regarding initial bodyweight and gender distribution. The infection rates found in both treatment groups were not significantly different (for Groups 1 and 2, respectively, 93.3% and 92.9% in kennel A; 70.0% and 77.7% in kennel B; 8.0% and 17.2% in kennel C). Table 1 summarises the average FECs recorded during the trial. In general (except for day 98) the mean egg counts for Group 1 were lower than for Group 2, and significantly lower on days 14 and 168. Except for days 56 and 70, the percentage of pups with positive FECs was higher for Group 2 than for Group 1 (Table 1; Fig. 1). In both groups, the number of positive FECs recorded for the pups of kennels A and B did not substantially diminish after weaning and relocation (Fig. 1).

For those animals showing positive FECs at 1 or more measuring days, the mean (*a*) AUC[t] values were 538.9 (±1561) and 943.0 (±1382) for Groups 1 and 2, respectively, the difference between the groups was of significance ($p = 0.0053$). In the non-inferiority analysis, the ratio of these mean (*g*) AUC[t] values was 5.14, i.e., Group 2 showed a 5.14 higher FEC than Group 1 ($p = 0.0062$; 90% confidence interval 1.972–

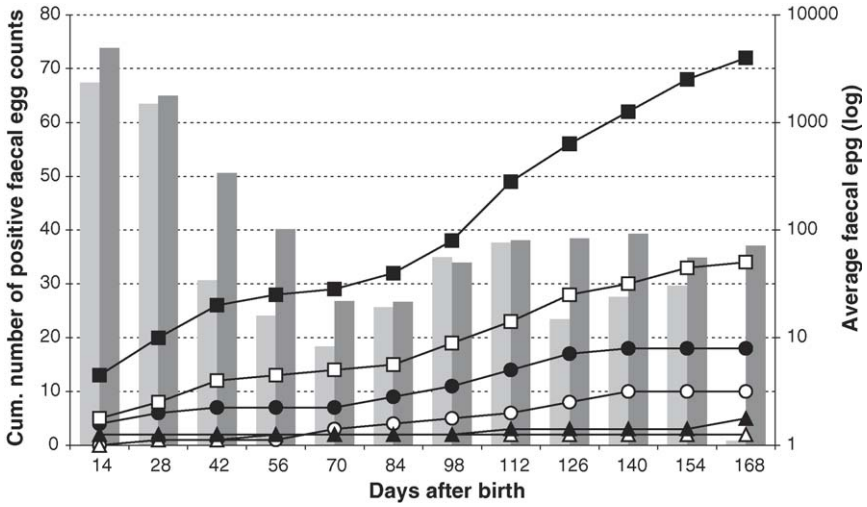

Fig. 1. Cumulative number of positive faecal egg counts and average faecal epg for pups in Group 1 (treated with milbemycin-based tablets) and Group 2 (treated with febantel–pyrantel embonate-based tablets) during the study. Bars: average faecal epg for Group 1 (light grey) and Group 2 (dark grey). Squares, circles or triangles: cumulative positive faecal egg counts for Group 1 (white) and Group 2 (black). Squares: kennel A pups (Harrier). Circles: kennel B pups (Beagle). Triangles: kennel C pups (various breeds).

13.384 including only values which were higher than the pre-specified margin of 0.7).

The number of reported adverse events for each treatment group was not significantly different (24 and 19 cases for Groups 1 and 2, respectively; $p = 0.3197$). Most events were of gastrointestinal nature. Out of these adverse events, two (one in each treatment group) were judged as probably and eight (four in each treatment group) as possibly caused by the treatment. All these cases represented pups from kennel C. The remaining cases started many days after the day of administration and were probably associated with the stress of weaning and relocation.

4. Discussion

Praziquantel is a known cestodicide without efficacy against ascarid worms (Andrews et al., 1983). Lufenuron is an insect growth development inhibitor approved for the control of fleas on dogs and cats not known to be effective against gastrointestinal worms. Consequently, the observed activity of both combination tablets against *T. canis* was considered not to be affected by these two components.

The similar infection rates observed for the animals in both treatment groups and in the three kennels indicate that the challenge levels were not substantially different for the groups, both before weaning (i.e., still in the kennel), or after weaning and relocation of most animals to private homes.

In previous investigations on pups, the number of *T. canis* worms was reduced by an average of 95.8% after treatment with a pyrantel pamoate suspension (Jacobs, 1987), and the egg output by 94.6–100% after treatment with febantel tablets (Christensson et al., 1991), and by 84.7–98.1% after treatment with tablets containing a combination of febantel, pyrantel embonate, and praziquantel (Fisher et al., 1994), always compared with untreated controls. However, these results cannot be directly compared with those in this present study because they were obtained with different treatment and measuring regimes and because we did not use untreated controls and consequently the relative reduction in the faecal egg output could not be determined. Nevertheless, the average FECs for Groups 1 and 2 at day 168 were 99.9% and 98.5%, respectively, lower than the corresponding initial FECs at day 14.

It is remarkable that the number of positive FECs for Harrier and Beagle pups did not diminish after weaning and relocation at week 8 (see Fig. 1). This illustrates the ease for pups to be infected with *T. canis* from non-maternal sources and the importance of adequate control to reduce the faecal output and thus the contamination of the environment.

Both products were well tolerated by the pups. This confirms the suitability of both treatment programmes for controlling *T. canis* infections in pups. However, the lower number of positive FECs and the lower average egg outputs determined for the pups in Group 1 suggest that the treatment programme with the milbemycin-based combination tablets was more efficacious than the alternative one with the febantel–pyrantel embonate tablets.

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