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Anthelmintic resistance of *Ostertagia ostertagi* and *Cooperia oncophora* to macrocyclic lactones in cattle from the western United States

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ABSTRACT

In June 2008, 122 yearling heifers with a history of anthelmintic resistance were obtained from pastures in northern California and transported to a dry lot facility in southwestern Idaho, USA. Fifty heifers with the highest fecal egg counts were selected for study enrollment. Candidates were equally randomized to treatment with either injectable ivermectin (Ivomec®, Merial, 0.2 mg kg^{-1} BW), injectable moxidectin (Cydectin®, Fort Dodge, 0.2 mg kg^{-1} BW), oral fenbendazole (Safe-Guard®, Intervet, 5.0 mg kg^{-1} BW), oral oxfendazole (Synanthic®, Fort Dodge, 4.5 mg kg^{-1} BW), or saline. At 14 days post-treatment, nematodes were recovered from the abomasum, small intestine, and large intestine. Parasitism was confirmed in the control group when 10/10 animals were infected with adult *Ostertagia ostertagi* and 9/10 animals with both developing and early L_4 stages of *O. ostertagi*. Similarly, 9/10 animals were parasitized with adult *Cooperia* spp. Fenbendazole and oxfendazole efficacy verses controls were >90% against adult *Cooperia* spp., while moxidectin caused an 88% parasite reduction post-treatment ($P < 0.05$). Ivermectin treatment resulted in no reduction in adult *Cooperia* spp. Based on geometric mean percent reduction versus saline controls, all four treatments were ≥90% efficacious against adults of *O. ostertagi*, while moxidectin and fenbendazole were equally effective against developing and inhibited early L_4 stages ($P < 0.05$). Ivermectin was not efficacious for developing or inhibited early L_4 stages of *O. ostertagi*. Oxfendazole failed to decrease *O. ostertagi* developing L_4 larvae by >90% but was efficacious for inhibited early L_4 larvae. Based on the results of this study, a source of multi-species anthelmintic resistance in cattle has been identified in the western United States.

1. Introduction

Gastrointestinal nematodes present a clinical and economic concern to cattle and producers, respectively. Lawrence and Ibarburu (2007) detailed the economic importance of anti-parasiticides to the United States beef industry. They demonstrated in a meta-analysis of over 170 published articles that removal of dewormers from the United States beef production chain would result in increased production costs of nearly $190 per head according to 2005 market prices. Given the importance of effective parasite control, there is heightened concern over reduced anthelmintic efficacy as reports of developing resistance have surfaced throughout the world including the United States, New Zealand, Brazil, Argentina, and the UK (Anziani et al., 2004; Gasbarre et al., 2005; Waghorn et al., 2006; Bliss et al., 2008; Demeler et al., 2008; Condi et al., 2009).

Currently, three major classes of anthelmintics are available for cattle including imidazothiazoles (levamisole), benzimidazoles (albendazole, fenbendazole, and oxfendazole), and macrocyclic lactones. Macrocyclic lactones are divided into two groups: first-generation

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Table 1
Randomization fecal EPG and body weights.

Treatment group (10 per group)	Moxid.	Iverm.	Fenben.	Oxfend.	Saline
Randomization fecal strongyle egg/g (EPG)					
Mean	81	76	77	70	72
Std. dev.	71.3	47.7	58.9	51.6	44.4
Range	27–268	30–166	31–226	22–178	32–170
Randomization individual body weight (kg)					
Mean	321	316	321	318	318
Std. dev.	20.0	32.8	27.6	20.4	14.8
Range	294–359	263–366	279–356	288–346	291–334

Moxidectin (Moxid.), Ivermectin (Iverm.), Fenbendazole (Fenben.), Oxfendazole (Oxfend).

avermectins (ivermectin, doramectin, eprinomectin, and abamectin), and second-generation milbemycins (moxidectin). For testing drug efficacy, the two most widely accepted methods are the fecal egg count reduction test (FECRT) and the controlled efficacy test. Although the FECRT is more commonly used, the most reliable and accepted gold-standard method is the controlled efficacy test (Coles et al., 2006). Whichever method is used, the 2001 VICH guidelines state that for a product to be acceptable, the calculated percent effectiveness should be at least 90% (Vercruysse et al., 2001).

The continued efficacy of the current anthelmintics for cattle has recently been questioned due to a number of parasite-resistance reports. In South America and New Zealand, resistance against all three classes of anthelmintics has been reported in cattle (Waghorn et al., 2006; Soutello et al., 2007; Suarez and Cristel, 2007; Condi et al., 2009). More recently, reduced drug efficacies and resistance to macrocyclic lactones have been reported in the United States (Smith and Gasbarre, 2004; Gasbarre et al., 2005; Bliss et al., 2008).

Data suggestive of anthelmintic resistance was collected in 2005 and 2006 at the authoring research facility. Briefly in 2005, 150 naturally infected yearling steers were obtained from a single source in northern California and treated with injectable long-acting moxidectin, injectable ivermectin, or saline. At the first sampling point 21 days post-treatment, the long-acting moxidectin group demonstrated a 98% reduction in fecal egg counts compared to a 69% reduction with injectable ivermectin. The Day 21 larval coproculture in the ivermectin group was 98% *Cooperia* spp. and 2% *Ostertagia ostertagi* compared to approximately 50% of each in the controls (Yazwinski et al., 2006).

The following year, the study authors conducted a controlled efficacy trial and compared two pour-on avermectins (doramectin and generic ivermectin) to saline controls (Edmonds et al., 2007). For this trial, 30 naturally infected crossbred steers were obtained from the same California source as described for the previous study (Yazwinski et al., 2006). The 2007 study results demonstrated that both doramectin and generic ivermectin were 64% efficacious against *Cooperia* spp. (adults and L_4 larvae combined) based on worm counts from samples collected at necropsy 14 or 15 days post-treatment. Doramectin pour-on was 94% efficacious against adult *O. ostertagi* and 69% efficacious against *O. ostertagi* developing and early L_4 larvae combined. The generic ivermectin pour-on was only 62% efficacious against adults and 0.1% efficacious against developing and early larvae combined (Edmonds et al., 2007).

Based on these previous study results, the current efficacy trial was initiated in 2008 to determine the effectiveness of anthelmintics from two different drug classes in cattle derived from the same California source. Specifically, two injectable macrocyclic lactones (ivermectin and moxidectin), along with two oral benzimidazoles (fenbendazole and oxfendazole), were tested.

2. Materials and methods

2.1. Study animals

In late June 2008, a total of 122 yearling heifers naturally infected with gastrointestinal nematodes were obtained from pastures in northern California, USA. Animals were obtained mid-summer because earlier studies at this research site had shown cattle were typically infected with a higher proportion of inhibited early L4 larvae of *O. ostertagi* at that time of year. Heifers were typical beef breeds for this region consisting of English and Continental crosses. The California source where the heifers originated was a large, approximately 22,000 acre property, used for beef cattle production. At this location, cattle were grazed on permanent pastures of native forages. Macrocyclic lactone anthelmintics had been used exclusively for at least the last four years. Typically, cattle were gathered from multiple sources and treated at turnout in November or December, and then again one to two more times during the grazing season with a pour-on macrocyclic lactone.

The yearling heifers were obtained and transported to the research feedlot in southwest Idaho, USA. Cattle were acclimated to dry lot confinement pens and fed a total mixed ration for nine days. During this time, animals were monitored for any signs of disease. On Day 7, all healthy candidates were processed, weighed, and sampled for determination of fecal strongyle egg count. At processing, animals were vaccinated for infectious bovine rhinotracheitis, bovine virus diarrhea types 1 and 2, respiratory syncytial virus, and parainfluenza-3 virus (Bovi-Shield Gold® 5, Pfizer Animal Health) along with *Clostridium chauvoei*, *Clostridium septicum*, *Clostridium haemolyticum*, *Clostridium novyi*, *Clostridium tetani*, and *Clostridium perfringens* types C and D (Covexin® 8, Schering-Plough Animal Health). The 50 heifers with the highest egg count (average 75 EPG, range 22–268 EPG) were selected for study inclusion. The selected heifers weighed on average 319 kg with a

range of 263 kg to 366 kg on Day 7. Table 1 provides the randomization average strongyle egg count and bodyweights per treatment group.

2.2. Animal allocation and treatment groups

Heifers were ranked in descending order by Day 7 strongyle egg counts and bracketed into replicates of five animals per group that yielded 10 groups (blocks). Within each block, the five animals were randomly assigned to treatment using a random number generator. The five treatments were injectable ivermectin (Ivomec®, Merial Inc., 0.2 mg kg^{-1} BW, SC), injectable moxidectin (Cydectin®, Fort Dodge Animal Health, 0.2 mg kg^{-1} BW, SC), oral fenbendazole (Safe-Guard®, Intervet Inc., 5.0 mg kg^{-1} BW), oral oxfendazole (Synanthic®, Fort Dodge Animal Health, 4.5 mg kg^{-1} BW), or saline. Saline was injected subcutaneously at the same dose volume as ivermectin and moxidectin. The 10 blocks were treated over a three-day window so that no more than 20 animals were necropsied on any one day. Blocks 1–3 were treated on Day 1, blocks 4–6 on Day 2, and blocks 7–10 on Day 3, with all blocks necropsied 14 days following treatment. All treatments were administered according to label directions and were dosed based on the individual body weight at the time of treatment. Feed and water were not withheld prior to dosing. Each animal was individually restrained in a hydraulic cattle chute and weighed on a certified scale. Drug doses for the injectable products were rounded to the next highest 0.2 mL increment while oral doses were rounded to the next highest 1.0 mL increment. Following treatment, animals were held for 14 days by block in dry lot pens. During the trial, animals were provided a total mixed ration and water ad libitum. The ration exceeded NRC requirements for beef cattle. At approximately 36 h prior to necropsy, feed was withheld to decrease gastrointestinal content at necropsy.

2.3. Parasitological procedures

Rectally obtained fecal samples were collected for determination of strongyle egg counts. A 3-g fecal sample was processed in a standard double centrifugation technique consisting of water followed by a saturated sucrose solution (1.2 sp gr). The total strongyle egg count for sucrose flotation to one coverslip was determined at 100x magnification. The total count was then divided by 3 to determine the number of eggs/g. Strongyle eggs were presumed to be those of *Cooperia*, *Ostertagia*, *Trichostrongylus*, *Haemonchus*, and *Oesophagostomum* genera.

At necropsy, the abomasum, small intestine, and proximal one meter of the large intestine were separated in situ, removed, and their contents collected separately into graduated containers. The luminal surface of each organ was rinsed and washings were added to the contents and brought to a known volume. Duplicate aliquots representing 5% each of the total contents were obtained from the abomasum and small intestine along with 20% aliquots from the large intestine. Samples were preserved in 10% w/v formalin for subsequent nematode enumeration and identification. Additionally, each abomasum was soaked in warm tap water for 24 h, washed, and 5% aliquots were preserved in 10% w/v formalin. Abomasum, abomasum incubates, and small intestine aliquots were washed over a 400-mesh (38 μm opening) sieve, and the large intestine aliquots were washed over a 200-mesh (75 μm opening) sieve. An entire 5% aliquot from each collection was examined and all parasites enumerated and identified. All nematodes were identified to genus, species (if possible), and stage.

2.4. Statistical analysis

Anthelmintic efficacy was determined using the VICH guidelines for anthelmintic efficacy (Vercruysse et al., 2001). Anthelmintic percent reduction for each nematode was determined using the following equation:

$$\frac{\text{control group geometric mean nematode no.} - \text{treated grp geometric mean nematode no.}}{\text{control group geometric mean nematode no.}} \times 100.$$

Analysis of variance was used to compare the log transformed worm counts (transformation = $\log_e(\text{count} + 1)$). Where the overall treatment effect was statistically significant ($P < 0.05$), pair-wise comparisons between groups were made (unadjusted alpha = 0.05). Statistical significance was declared if $P < 0.05$ (SAS®, SAS Institute, Cary, NC).

3. Results

Following analysis of the preserved organ aliquots, all 10 controls were parasitized with adult and larval stages of *O. ostertagi* and 9/10 with adult *Cooperia* spp. Only one control animal was infected with larval stages of *Cooperia* spp., thus preventing efficacy analysis by VICH guidelines (Vercruysse et al., 2001). The male *Cooperia* spp. were identified as 98% *Cooperia oncophora* and 2% *Cooperia surnabada*. A few animals were infected with *Haemonchus placei*, *Trichostrongylus axei*, *Ostertagia lyrata*, *Oesophagostomum radiatum*, *Nematodirus helvetianus*, and *Trichuris discolor*. However, efficacy analysis was not conducted because an insufficient proportion of control animals were found to be harboring these species and the worm numbers recovered from individual animals did not meet adequacy of infection minimums.

Table 2 provides the geometric and arithmetic mean numbers of *O. ostertagi* adults, developing L_4 larvae, and inhibited early-L_4 larvae recovered from all five treatment groups at necropsy. Table 2 also lists the range, number of positive animals per treatment group, and geometric percent reduction in total worm burden versus controls. The average percent and range of total L_4 larvae *O. ostertagi* recovered from each animal is also presented. All four treatments significantly decreased *O. ostertagi* adults by approximately 90% or more compared to controls. Moxidectin, fenbendazole, and oxfendazole treatment also significantly reduced adult *O. ostertagi* compared to treatment with ivermectin. A sta-

Table 2
Recovery of *Ostertagia ostertagi* per treatment group on Day 14.

Treatment group (10 per group)	Moxid.	Iverm.	Fenben.	Oxfend.	Saline
Adults					
Geometric mean	0.00[b]	62.66[c]	1.49[b]	1.10[b]	603.90[a]
Arithmetic mean	0	642	6	8	1226
Range	0–0	0–4680	0–20	0–40	80–3280
No. of positives	0	8	3	2	10
Geometric reduction (%)	100	89.6	99.8	99.8	
Developing L_4					
Geometric mean	1.05[c]	24.48[a]	1.86[bc]	15.58[ab]	87.09[a]
Arithmetic mean	8	346	38	160	462
Range	0–60	0–2820	0–200	0–1260	0–2620
No. of positives	2	7	2	6	9
Geometric reduction (%)	98.8	71.9	97.9	82.1	
Early L4					
Geometric mean	11.97[b]	35.76[ab]	2.41[b]	5.69[b]	302.69[a]
Arithmetic mean	212	6502	92	1762	4428
Range	0–1080	0–63620	0–500	0–17100	0–24180
No. of positives	5	6	2	3	9
Geometric reduction (%)	96.0	88.2	99.2	98.1	
Percent total O. ostertagi per animal that is L_4 stages					
Group arithmetic mean	100%	52%	65%	99%	46%
Range	100%	8.3–96%	0–97%	94–100%	0–90%
Total no. of positives	5	8	3	6	10

Moxidectin (Moxid.), Ivermectin (Iverm.), Fenbendazole (Fenben.), Oxfendazole (Oxfend).
For geometric means, values in the same row with no superscript in common are significantly different from each other at $P < 0.05$.

tistically significant decrease in developing *O. ostertagi* L_4 larvae was observed only following treatment with moxidectin and fenbendazole, with a 98.8% and 97.9% reduction, respectively. The percent reduction in developing L_4 *O. ostertagi* larvae following treatment with either ivermectin or oxfendazole was less than 90% and not statistically different than the controls. The inhibited early-L_4 larvae of *O. ostertagi* were significantly reduced greater than 90% by moxidectin (96.0%), fenbendazole (99.2%), and oxfendazole (98.1%). The percent reduction in inhibited early L4 larvae following treatment with ivermectin (88.2%) was not statistically different than the controls.

Table 3 provides the geometric and arithmetic mean numbers of adult *Cooperia* spp. recovered at necropsy. Moxidectin, fenbendazole, and oxfendazole treatment resulted in a significant decrease in total adult *Cooperia* spp. worm burden. Treatment with either benzimidazole product resulted in a 100% reduction in adult *Cooperia* spp., while moxidectin produced an 87.9% reduction. No decrease in adult *Cooperia* spp. was found after treatment with ivermectin.

4. Discussion

The results from this controlled efficacy trial support our prior findings of macrocyclic lactone resistance in cattle obtained from a single source in northern California, USA (Yazwinski et al., 2006; Edmonds et al., 2007). In the current study, ivermectin was not efficacious against developing or early L_4 stages of *O. ostertagi*. This finding is consistent with our previous trial where both generic ivermectin and doramectin were also less than 90% effective for developing and early L_4 stages of *O. ostertagi*. In this previous trial, generic ivermectin was only 62% efficacious for adult stages whereas doramectin efficacy was 94% (Edmonds et al., 2007). The efficacy difference between the generic and parent pharmaceuticals to *O. ostertagi* was likely due to variations in the product preparations (Lifschitz et al., 2004; Yazwinski et al., 2004). In the current study, ivermectin was the least effective treatment against adult *O. ostertagi* producing an 89.6% reduction and only minimally reaching the 90% threshold set by the VICH guidelines. Coles et al. (2006) states that when the efficacy is expected to be ≥99%, anthelmintic resistance is confirmed when efficacy is <95% based on arithmetic means. Using this standard, ivermectin was not effective against adult *O. ostertagi*. To date, these study authors are unaware of any other controlled efficacy studies documenting avermectin resistance to *O. ostertagi* in naturally infected cattle. Van Zeveren et al. (2007) reported the development of a laboratory derived ivermectin resistant isolate of *O. ostertagi* following repetitive exposure to subtherapeutic and therapeutic levels of ivermectin. Suspected emerging resistance has been reported in New Zealand and Argentina but those findings are unconfirmed (Waghorn et al., 2006; Suarez and Cristel, 2007).

In the current study, fenbendazole was efficacious for adult and larval stages of *O. ostertagi* while oxfendazole was efficacious for the adult and inhibited early L_4 stages but not for developing L_4 larvae. Williams (1991) and Miller et al. (1988) reported considerable variability with the efficacy of fenbendazole and oxfendazole for the inhibited early L_4 stage of *O. ostertagi*. This inconsistency was often due to wide efficacy variability between individual animals (Williams, 1991). It is noteworthy that cattle obtained from this single source had no history of benzimidazole treatment.

Table 3
Recovery of adult *Cooperia* spp. per treatment group on Day 14.

Treatment group (10 per group)	Moxid.	Iverm.	Fenben.	Oxfend.	Saline
Geometric mean	16.12[c]	522.96[a]	0.00[b]	0.00[b]	132.92[a]
Arithmetic mean	312	730	0	0	520
Range	0–2380	120–1680	0	0	0–2480
No. of positives	5	10	0	0	9
Geometric reduction (%)	87.9	−293.4	100	100	

Moxidectin (Moxid.), Ivermectin (Iverm.), Fenbendazole (Fenben.), Oxfendazole (Oxfend).
For geometric means, values in the same row with no superscript in common are significantly different, $P < 0.05$. Male *Cooperia* were approximately 98% *C. oncophora* and 2% *C. surnabada*. On Day 14 on only one animal, in the saline group, was positive for 20 *Cooperia* spp. L_4 larvae.

A number of rationales have been postulated for the lack of reported *O. ostertagi* anthelmintic resistance in cattle when compared to *Cooperia* spp. (Van Zeveren et al., 2007). Some theories include that adult *O. ostertagi* are short lived (25–50 days), produce few eggs, and are exposed to higher drug concentrations in the abomasum mucosa compared to the small intestine. Another rationale, which is supported by this study, is the lack of accurate detection. Most reports of resistance are first identified based on a lack of fecal strongyle egg count reduction following treatment. Condi et al. (2009) found that, due to egg suppression post-treatment, the fecal egg count reduction test (FECRT) provided an under-estimation of anthelmintic resistance when compared to necropsy results. In the present study, all treatments reduced adult *O. ostertagi* by at least 89.6%. Accordingly, while not performed, it is reasonable to assume that if only fecal strongyle egg counts had been performed on Day 14, the fecal egg counts for the ivermectin group would have been low, suggesting ivermectin efficacy. This assumption is supported by the results from the study authors' 2005 study wherein ivermectin treatment resulted in a 69% egg count reduction and larval coprocultures consisted of 98% *Cooperia* spp. and 2% *Ostertagia* spp. In the current and 2006 efficacy studies we found that even though adult *O. ostertagi* were reduced by approximately 90%, some cattle still carried significant numbers of developing and inhibited early L_4 larvae. Since larval stages of *O. ostertagi* remained following treatment with macrocyclic lactones, a greater selection pressure was likely placed on these stages.

In addition, neither ivermectin nor moxidectin were efficacious against adult *Cooperia* spp. consisting predominately of *C. oncophora*. The identification of macrocyclic lactone resistant *C. oncophora* correlates with its role as one of the dose-limiting species and the suggestion that it would be the first genus to show macrocyclic lactone resistance (Van Zeveren et al., 2007). In the authors' previous study, we observed apparent *Cooperia* spp. resistance to the avermectins but not to a milbemycin based on fecal egg count percent reductions (Yazwinski et al., 2006). In Brazil, Condi et al. (2009) recently demonstrated moxidectin resistance in *C. punctata*, *C. pectinata*, *O. radiatum*, and *Trichuris* spp. all arising from the same source. Furthermore, macrocyclic lactone resistant *Haemonchus contortus* and *Cooperia* spp. have been identified in the United States (Gasbarre et al., 2005).

Based on the results of the current trial, evidence is provided on ivermectin resistance to *O. ostertagi*. In addition, a case of *C. oncophora* macrocyclic lactone resistance has been identified. Additional controlled efficacy trials are needed to determine the extent of anthelmintic resistance in the western United States.

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