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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