Treatment of Subclinical Nematodiasis in Idaho Stocker Cattle With Cydectin Long-Acting Injectable or Ivomec Injectable

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ABSTRACT

The current study was conducted to obtain regional data on Cydectin® Long-Acting (LA) Injectable administered to cattle subcutaneously in the dorsal aspect of the ear at the rate of 1.0 mg moxidectin/kg body weight (bw) in regard to: 1) safety; 2) ease of administration; and 3) effectiveness relative to Ivomec® Injectable (0.2 mg ivermectin/kg bw). To that end, 50 naturally infected yearling stocker steers were treated with Cydectin LA, Ivomec, or left as non-treated controls, and then grazed as a single group of 150 animals on permanent pasture for 150 days. At several time points during the study, injection sites were inspected for any reaction (Cydectin LA animals only) and all animals were weighed and fecal-sampled (nematode egg counts and coprocultures). Rates of gain for Cydectin LA-treated cattle were significantly greater than control animal rates for trial day intervals 0-21, 100-150, and 0-150. Ivomec-treated and control animals gained weight at equivalent rates for all study intervals. Average gains by treatment group for the entire study were 121.7, 116.9, and 110.4 kg for Cydectin LA, Ivomec, and control animals, respectively. For all post-treatment sample dates, fecal egg counts for Cydectin LA-treated cattle were significantly ($P < 0.05$) lower than counts for either of the other 2 groups. Mean treatment group, fecal egg count reductions were >90% for Cydectin LA through Day 50, but never above 72% for Ivomec. Percentages of coproculture larvae as *Cooperia* spp were significantly ($P < 0.05$) elevated above concurrent control animal values through Day 50 for Ivomec-treated cattle and through Day 100 for Cydectin LA-treated cattle. All Cydectin LA injections were easily administered with adverse reactions limited to a slight swelling at the injection site of 2 of the 50 Cydectin LA animals; reactions were completely resolved by Day 100. Cydectin LA was demonstrably effective in the treatment and prophylaxis of subclinical bovine nematodiasis. *Cooperia* spp infections

appeared to be the least effectively controlled by the 2 products evaluated in this study, an observation consistent with macrocyclic lactone usage. These infections should be afforded specific consideration at both the farm and research levels relative to current and future endectocide usage in cattle.

INTRODUCTION

Parasite gastroenteritis (PGE) is an omnipresent pathologic condition of most cattle with multiple agents, etiologies, and degrees of detriment. The offending agents are primarily protozoan (*Eimeria* spp) and helminth (nematode, trematode, and cestode). Given the consistent nature of PGE and the non-tenable objective of complete protection for grazing animals, measures of chemical control are practiced for therapeutic action (treatment for ongoing PGE), prophylactic action (treatment for prolonged avoidance of economically apparent disease), or a combination of the 2 measures. In regard to nematode infections, several chemicals provide solely therapeutic activity wherein existing worm burdens are removed to a variable degree (eg, oxfendazole, albendazole, fenbendazole, and levamisole). Additional chemicals possess not only therapeutic activity, but also remnant efficacies wherein certain challenge infections encountered post-treatment are prohibited for variable periods of time (ie, the macrocyclic lactones: doramectin, eprinomectin, ivermectin, and moxidectin).[1]

At the time of their initial commercial clearances, none of the above parasiticides were 100% effective against all label-inscribed nematodes, nor were they 100% effective for all stated periods of persistent efficacy. In addition, resistance has subsequently emerged in certain nematode populations against products of all compound classes now available for use in cattle.[2] As a result, spectra of activities, efficacies, and periods of protection afforded by bovine nematocides today are not as extensive or apparent as they were in years past.

To enhance efficacy and persistence, moxidectin, the active ingredient of Cydectin® Pour-On and Cydectin® Injectable (Fort Dodge Animal Health), has been formulated into an oil-based, 10% w/v solution for subcutaneous injection into the dorsal surface of the ear at the rate of 1.0 mg moxidectin/kg body weight (bw) (Cydectin® Long-Acting [LA] Injectable). In earlier studies, Cydectin LA was found to be highly effective in the immediate and persistent (100-150 day) control of both external[3] and internal[4] parasites of cattle. The product was also shown to be safe and effective in field studies targeting nematode infections, and in addition, responsible for significant weight gain advantages of treated animals over controls.[5,6]

In addition to providing regional data on the safety, facility, and effectiveness of Cydectin LA in comparison to Ivomec® Injectable (Merial), the current study was undertaken with 2 overriding objectives: 1) to further evaluate the utility of chemotherapy for subclinical bovine nematodiasis, especially in light of the current concern over drug failure in cattle[7]; and 2) to discern any definite patterns of nematode re-establishment within 150 days of Cydectin LA administration. Such infections might potentially reduce the overall benefit of this product, a scenario that should be avoided given the potential benefits of Cydectin LA usage and the industry reliance on macrocyclic lactone endectocides for animal welfare and productivity.

MATERIALS AND METHODS

Study Animals and Management

All animals were naturally infected, stocker-type yearling steers (12-14 months of age at study initiation) of predominately Angus breeding. The cattle originated in California and were delivered to the Idaho research facility 20 to 40 days prior to the start of the study for acclimation and observation.

During acclimation and for the duration of the study (April 19, 2005, through

September 16, 2005), the animals were pastured as 1 group at the effective stocking rate of 3 animals per acre. The entire 50-acre pasture of irrigated fawn fescue and clover was cross-fenced into 1- to 2-acre subplots and the cattle (as a single group) were rotated between subplots every 2 days, with a complete rotation to all subplots requiring approximately 50 days. Pasture growth was more than adequate in the provision of ad libitum grazing and the animals were additionally provided free-choice salt/mineral supplement and water.

All animals were observed daily for overall health as well as reactions to experimental treatments. In the course of the study, infectious bovine keratoconjunctivitis was observed and treated (Biomycin 200®, Boehringer-Ingelheim) in 3 control and 4 Ivomec-treated animals, and foot-rot was observed and treated (Biomycin 200®, Boehringer-Ingelheim) in 2 control, 1 Ivomec-treated, and 1 Cydectin LA-treated animal. All treatments for the above extraneous infections were entirely successful.

Animal Allocation and Treatment Groups

On Day -1, all candidate cattle were weighed and a uniform set of 150 steers were selected. The animals were ranked by eggs per gram of feces (EPG) counts attained during acclimation, bracketed into replicates (3 animals of most similar egg counts per replicate), and treatment groups randomly assigned within each replicate. In total, 50 animals were assigned by the above, restricted scheme of allocation to each of the 3 experimental groups: 1) control (no treatment or placebo); 2) Ivomec 1% Injectable (ivermectin 0.2 mg/kg bw given via subcutaneous injection of the commercial product in front of the shoulder at the rate of 0.02 mL/kg bw); and 3) Cydectin LA (1.0 mg moxidectin/kg bw given via subcutaneous injection of the 10% w/v oil-based product in the dorsal aspect of the proximal one third of the ear and near the auricular ring of cartilage at the rate of 0.01 mL/kg bw). Animals were treated on Day 0 according to allocation, the manufacturers' prescribed dosage rates, and Day -1 body weights. All per-animal treatment volumes were rounded to the next highest 0.5 mL increment.

Trial Schedule

Animal acclimation was conducted for a minimum of 20 days immediately prior to Day -1. Animals were weighed on Days -1, 0, 21, 50, 100, 149, and 150. Fecal samples were obtained from each animal on all above trial days with the exception of Days -1 and 150. Cydectin LA injection sites were palpated for all treatment group animals on Day 21 and subsequently on Days 50, 100 and 149 for those animals with a noted swelling on the previous inspection date. Daily throughout the study, all animals were observed for overall health and adverse reactions to treatment.

Parasitological Procedures

All determinations of strongyle EPG of feces were conducted via standard laboratory procedure utilizing double centrifugation (water followed by saturated sucrose solution [1.2 sp gr]) of 3-g samples, all sucrose flotation to one coverslip, and then examination of the total slide-mounted coverslip at 100× for the total egg count. The total count was then divided by 3 in order to obtain the EPG count. Strongyle eggs are those of *Cooperia*, *Ostertagia*, *Trichostrongylus*, *Haemonchus*, and *Oesophagostomum* genera.

In order to estimate the proportions of the strongyle EPG counts attributable to the above genera, a laboratory standard coproculture procedure was employed. For each fecal sample with an EPG value >5, approximately 20 g of feces were mixed with an equal volume of ground corncob and water to achieve a suitable consistency. The coproculture was then kept at 27°C for 14 days, at which time it was flooded with water for the harvest of infective third-stage larvae. The larvae from each sample were then concentrated, killed in heated 10% for-

malin, and examined at 100× magnification for larvae identification to genus and counting (total larvae or the first 100 per sample, whichever came first). The above procedure was employed on individual fecal samples for all post-treatment dates, but by treatment group composite coprocultures for Day 0 fecal samples.

Statistical Analysis

The experimental design was a randomized complete block. Response variables were the fecal egg counts, coproculture larval percentages, and periodic weight gains. Prior to analysis of variance, EPG counts were transformed to the $\log_{10}$ (X +1) for data normalization. Standard analysis of variance (ANOVA) was utilized to determine treatment effect (SAS®, SAS Institute, Cary, NC). For all analysis with an overall significant F ($P < 0.05$), treatment group least squares means were compared by 2-sided t-tests, again, at the 5% level of probability.

RESULTS

Mean animal body weights by treatment group and study day are presented in Table 1. No significant differences were noted during the trial. Mean animal daily gains by treatment group and study interval are presented in Table 2. Rates of gain for Cydectin LA-treated animals were significantly ($P < 0.05$) greater than rates for control animals for trial day intervals 0-21, 100-150, and 0-150. Ivomec-treated cattle did not gain weight at rates that were significantly greater than the control group for any trial interval. Over the entire study, rates of gain were improved over control cattle by 5.4% and 9.5% for Ivomec- and Cydectin LA-treated cattle, respectively.

Strongyle EPG geometric means by treatment group and study day are presented in Table 3. All counts were similar on Day 0. For every post-treatment sample date, counts for Cydectin LA-treated cattle were significantly ($P < 0.05$) lower than counts for either of the other 2 groups. Ivomec-treated cattle EPG counts were significantly lower than control cattle counts on Days 21, 50, and 150.

Coproculture larval percentages by treatment group and study day are presented in Table 4. Percentages were similar among groups on Day 0, with >90% of the larvae of *Cooperia* and *Ostertagia* genera, a distribution that was consistent for the control group for the entire study. No coprocultures were conducted on Day 21 fecal samples from Cydectin LA-treated calves since respective EPG counts were not high enough for sufficient larval harvests. On Days 50 and 100, *Cooperia* spp larvae were predominate for Cydectin LA-treated cattle, and of significantly greater percentages than were observed for the control cattle ($P < 0.05$). A post-treatment preponderance of *Cooperia* spp larvae was seen for Ivomec-treated cattle as well, with *Cooperia* spp percentages greater than control cattle values through Day 50. Correspondingly, *Ostertagia* larvae percentages were significantly reduced from control cattle levels for 100 days (Cydectin LA) and 21 days (Ivomec). Combined *Haemonchus*, *Trichostrongylus*, and *Oesophagostomum* mean larval percentages never exceeded 8% for any treatment group during the study.

All treatments were easily administered in this study. Adverse reactions to treatment were limited to mild swelling (approximately 10 mL in volume) at the Cydectin LA injection sites of 2 animals; swellings were totally resolved by Day 100.

Table 1. Mean Animal Body Weights (kg) by Day of Study and Treatment Group.

Treatment Group	Day of Study				
	0*	21	50	100	150†
Cydectin LA	306.3	325.5	363.3	402.9	428.0
Ivomec	307.4	323.7	362.6	401.4	424.3
Control	307.7	323.1	359.1	397.9	418.1
SE	3.0	3.2	3.3	3.9	3.9

SE = standard error.
*Mean of Days -1 and 0.
†Mean of Days 149 and 150.

Table 2. Mean Animal Gains (kg/d) by Study Day Interval and Treatment Group.

Treatment Group	Study Day Interval				
	0-21	21-50	50-100	100-150	0-150
Cydectin LA	0.91[a]	1.26	0.79	0.50[a]	0.81[a]
Ivomec	0.78[ab]	1.30	0.78	0.46[ab]	0.78[ab]
Control	0.74[b]	1.20	0.78	0.40[b]	0.74[b]
SE	0.06	0.04	0.03	0.03	0.02

SE =- standard error.
[a,b]Means in the same column with different superscripts are significantly different ($P < 0.05$).

Table 3. Strongyle EPG Counts (geometric means) by Day of Study and Treatment Group.

Treatment Group	Day of Study				
	0	21	50	100	150
Cydectin LA	36.5[a,1]	0.8[c,4]	2.2[c,4]	4.7[b,3]	8.5[c,2]
Ivomec	25.5[a,1]	8.0[b,3]	17.0[b,1,2]	11.7[a,2,3]	14.7[b,2]
Control	35.8[a,1]	40.5[a,1]	27.8[a,1,2]	9.7[a,3]	21.6[a,2]

[a,b,c]Means on the same column with unlike superscripts are different ($P < 0.05$).
[1,2,3,4]Means in the same line with unlike superscripts are different ($P < 0.05$).

Table 4. Coproculture Larval Percentages by Treatment Group and Study Day (SE).

Genus/Day	Treatment Group		
	Cydectin LA	Ivermectin	Control
Cooperia			
-Day 0	58.0	60.0	63.0
-Day 21	—	98.0 (6.0)[a]	48.6 (4.7)[b]
-Day 50	88.7 (10.6)[a]	62.8 (5.9)[b]	44.7 (5.6)[c]
-Day 100	98.7 (7.9)[a]	37.3 (5.9)[b]	30.3 (6.0)[b]
-Day 150	71.5 (11.3)	41.9 (9.2)	51.9 (8.5)
Ostertagia			
-Day 0	34.0	33.0	33.0
-Day 21	—	2.0 (6.0)[b]	50.2 (4.7)[a]
-Day 50	10.0 (10.3)[b]	37.0 (5.7)[a]	51.3 (5.4)[a]
-Day 100	0.9 (7.7)[b]	59.6 (5.8)[a]	66.5 (5.9)[a]
-Day 150	28.0 (10.8)	55.8 (8.8)	45.1 (8.2)
Other			
-Day 0	8.0	7.0	4.0
-Day 21	—	0.0	1.2
-Day 50	1.3	0.2	4.0
-Day 100	0.4	3.1	3.2
-Day 150	0.5	2.3	3.0

— = insufficient number of samples with adequate number of eggs for culturing.
[a,b,c]Means on the same line with unlike superscripts are different ($P < 0.05$).

DISCUSSION

Results from the current study elucidate the effectiveness and beneficial effects of 2 endectocidal, macrocyclic lactone products in the treatment of subclinical nematodiasis in yearling stocker cattle. Based on post-treatment EPG reductions and average daily gains, Cydectin LA was measurably of greater effectiveness and benefit than Ivomec Injectable; results that could have been predicted given the dosage rates of the active ingredients and the expected periods of persistent efficacy for the 2 products.[8,9] Ivomec Injectable failed to reduce strongyle EPG counts by >90% at any time point post-treatment (an indication of non-efficacious activity[10]), and average daily gains of control and Ivomec Injectable treatment group cattle were statistically equivalent throughout the study. Animal treatment with Cydectin LA resulted in fecal egg counts that were significantly lower than those seen for control or Ivomec treated calves for the entire study. Also, weight gains for Cydectin LA-treated animals were significantly improved over controls for the first and final weigh periods of the study plus the total study time frame.

The parasite infections of the cattle were mixed, with coproculture larvae evenly distributed between *Ostertagia* and *Cooperia* genera at trial initiation and in the control cattle for the trial duration. After either treatment, nematode patencies, as roughly quantified by coproculture, were primarily Cooperiad. This was most demonstrable following treatment with Cydectin

LA wherein 98.7% of the fecal nematode eggs being passed at Day 100 were Cooperiad. The *Cooperia* species have been previously cited as being the most refractory of the cattle nematodes to the effects of the macrocyclic lactones.[11] Innate tolerance of the genus to macrocyclic lactones was recognized during the early screening of avermectins when it was shown that both *Cooperia* and *Nematodirus* were dose-limiting nematode genera for ivermectin.[12] *Nematodirus* spp infections are for the most part controlled in healthy animals by an effective immune response and are primarily of consequence on dairy operations,[13] and as such are not considered of major dimension in cattle production. *Cooperia* burdens, primarily of the species *oncophora*, *pectinata*, and *punctata*, are of great prevalence, magnitude, and impact in cattle less than 3 years of age and produced in temperate climates.[14] Failure of a compound to provide therapeutic control of cooperiasis is therefore of some significance. Macrocyclic lactones are being cited at an increasing rate for failure to control the *Cooperia* species in cattle.[15,16] In order to sustain the overall therapeutic effectiveness of macrocyclic lactones, the use of unrelated compounds for nematocidal therapy has been advocated if detrimental *Cooperia* infections are ongoing or imminent.[17] In the current study, and in several others conducted to determine the effectiveness of Cydectin LA in cattle,[6,18] *Cooperia* spp patencies were of foremost presence through most of the 150-day post-treatment periods, an occurrence that presumably might serve to propagate *Cooperia* populations selected for resistance and perhaps, increased pathogenicity.[19] It appears prudent, therefore, that the use of Cydectin LA or any other long-acting macrocyclic lactone be coupled with the use of an unrelated compound at some time point post treatment so as to restrict the propagation of resistant *Cooperia* spp burdens. In the words of 2 other groups of researchers, "resistance in nematode parasites in cattle is now becoming much more prominent and an informed opinion is that the situation for anthelmintic resistance in cattle parasites is about a decade behind that for parasites of sheep and goats,"[20] and "rather than ignore the development of resistance, as largely happened with nematodes of sheep, it is hoped that serious attempts will be made to try to prevent its rapid spread and development in cattle."[21]

Ivomec Injectable has been a boon for the cattle industry since the 1980s, with a history of immeasurable improvement in animal health and productivity. However, as a consequence of the extensive usage of ivermectin in its many commercial forms (original versus generic, parenteral versus oral), the effectiveness of ivermectin and related macrocyclic lactones has been predictably diminished through nematode selection for resistance.[11] Cydectin Long-Acting Injectable provides for the enhanced effectiveness of a macrocyclic lactone over what is currently available via the elevated dosage rate of moxidectin coupled with formulation for long-term delivery. In order to safeguard the effectiveness of Cydectin LA and other, envisioned long acting macrocyclic lactone preparations (eg, Eprinomectin Long-Acting Injection[22]), nematode burdens that arise due to extensive macrocyclic lactone use must be monitored and effectively removed. No nematocidal compounds unrelated in structure or mode of action to those currently available are being aggressively developed for commercial use in cattle. The compounds available now are therefore the only ones that will be available for some time to come, necessitating the preservation of their efficacies. Hopefully, as new formulations become available, they will be utilized with a keen awareness to the fragility of their efficacious and commercial lives.

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