Veterinary Parasitology 252 (2018) 157–162

Contents lists available at ScienceDirect

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Short communication

Concurrent treatment with a macrocyclic lactone and benzimidazole provides season long performance advantages in grazing cattle harboring macrocyclic lactone resistant nematodes

M.D. Edmonds[a,*], A.F. Vatta[b], A.A. Marchiondo[b,1], H.B. Vanimisetti[b], J.D. Edmonds[a]

[a] Johnson Research LLC, 24007 Highway 20-26, Parma, ID, 83660, USA
[b] Zoetis Inc., 333 Portage St., Kalamazoo, MI, 49001, USA

ARTICLE INFO

Keywords:
Anthelmintic resistance
Cattle
Nematodes
Efficacy
Benzimidazole
Macrocyclic lactone

ABSTRACT

In 2013, a 118-day study was initiated to investigate the efficacy of concurrent treatment at pasture turnout with an injectable macrocyclic lactone with activity up to 28 days and an oral benzimidazole, referred to as "conventional" anthelmintics, when compared to treatment with conventional macrocyclic lactone alone or an injectable macrocyclic lactone with extended activity of 100 days or longer. A group of 210 steers were obtained from a ranch in California and transported to Idaho, USA. A total of 176 steers with the highest fecal egg counts were blocked by pre-treatment body weights and pasture location. A total of 44 pasture paddocks were assigned with 4 steers per paddock with 12 paddocks per therapeutic treatment group and 8 paddocks per controls. The four treatments were injectable doramectin (Dectomax®, Zoetis Inc., 0.2 mg kg^{-1}BW, SC), injectable doramectin concurrently with oral albendazole (Valbazen®, Zoetis Inc., 10 mg kg^{-1}BW, PO), extended release injectable eprinomectin (LongRange™, Merial Limited, 1 mg kg^{-1}BW, SC) or saline. Cattle were individually weighed and sampled for fecal egg count on Days 0, 31/32, 61, 88, and 117/118 with an additional fecal sample on Day 14. At conclusion, one steer per paddock was euthanized for nematode recovery. The results from the first 32 days found evidence of macrocyclic lactone resistance against injectable doramectin and extended release eprinomectin. During this period the concurrent therapy provided nearly 100% efficacy based on fecal egg count reduction and a 19.98% improvement in total weight gain compared to controls ($P = 0.039$). At the conclusion of the 118-day study and past the approved efficacy for the conventional anthelmintics, the concurrent therapy with conventional anthelmintics provided a 22.98% improvement in total weight gain compared to controls ($P = 0.004$). The 118-day improvement in weight gain for the extended release eprinomectin group (29.06% compared to control) was not statistically different from the concurrent therapy with conventional anthelmintics. The results indicate that concurrent treatment with a conventional macrocyclic lactone and benzimidazole may provide production benefits early in the grazing period that continue throughout the entire period for cattle harboring macrocyclic lactone resistant nematodes. By using two different anthelmintic classes together, macrocyclic lactone resistant parasites were effectively controlled early in the period. Furthermore, the use of an effective conventional anthelmintic treatment regimen without an extended period of drug release may help to promote refugia and decrease the further selection for anthelmintic resistant parasites.

1. Introduction

The importance of gastrointestinal nematode control for the cattle industry is well recognized (Lawrence and Ibarburu, 2007). Control has generally been accomplished through the use of macrocyclic lactones including first-generation avermectins (ivermectin, doramectin, and eprinomectin) and second-generation milbemycins (moxidectin) (McArthur and Reinemeyer, 2014). These products are available in injectable and pour-on formulations that usually have less residual activity against the major gastrointestinal nematodes of cattle. In addition, oral benzimidazoles (albendazole, fenbendazole, and oxfendazole) and imidazothiazoles (levamisole) anthelmintics are available as well. These oral products have no residual activity and have historically seen limited use in the United States due to the availability of efficacious pour-on macrocyclic lactones (Gasbarre, 2014). Due to the short-acting properties of injectable and pour-on macrocyclic lactones,

* Corresponding author.
E-mail address: mattedmonds@johnsonresearchllc.com (M.D. Edmonds).
[1] Present address: Adobe Veterinary Parasitology Consulting LLC, Santa Fe, NM, 87506, USA.

https://doi.org/10.1016/j.vetpar.2018.02.009
Received 15 November 2016; Received in revised form 23 January 2018; Accepted 2 February 2018

animal health pharmaceuticals have worked with different delivery modalities in an effort to extend the efficacy period of these treatments (Cleale et al., 2004; Forbes, 2013). Recently, approval was granted in the United States for an extended release injectable eprinomectin that has a gastrointestinal nematode efficacy claim of 100–150 days depending on the nematode species (Soll et al., 2013).

A growing problem for the United States cattle industry is anthelmintic resistance to the commonly used macrocyclic lactones (Gasbarre, 2014; Gasbarre et al., 2009; Edmonds et al., 2010). This problem has developed due to multiple issues but continues to increase in importance with macrocyclic-lactone-resistant *Cooperia* spp. and *Haemonchus* spp. now common in many stocker operations (Gasbarre, 2014). The relative limited use of the benzimidazoles and imidazothiazoles in the United States has left resistance to these drugs far less common (Gasbarre, 2014). As a result, the concurrent treatment with a macrocyclic lactone and either a benzimidazole or imidazothiazole is widely promoted (Gasbarre, 2014). Some studies have shown these concurrent therapies, often referred to as combination treatments, can be efficacious in the face of widespread resistance (Walker et al., 2013; Fazzio et al., 2014). A modeling study (Leathwick, 2013) argued that treatment with anthelmintics of different drug classes concurrently would be superior for preventing the development of anthelmintic resistance when compared to regular rotation with different drug classes. This was based on the fact that use of two different classes at one time removes resistant parasites that might otherwise survive a one class treatment. In a second modeling study of ovine anthelmintic resistance development in Australia, the authors found that use of a more effective anthelmintic correlated with delayed development of anthelmintic resistance (Cornelius and Jacobson, 2016). In this modeling study, use of a drench that was > 99% efficacious over a drench that was 97% efficacious extended the time to anthelmintic resistance from less than seven years to more than 16 years in a low refugia environment with high resistance selection.

The current study was initiated to investigate gastrointestinal nematode control and performance efficacy of concurrent treatment at pasture turnout with an injectable macrocyclic lactone with activity up to 28 days (doramectin) and an oral benzimidazole (albendazole), referred to as “conventional” anthelmintics here for convenience, compared to a single treatment with either a conventional macrocyclic lactone (doramectin) or an injectable macrocyclic lactone with extended activity of 100 days or longer (extended release eprinomectin) during a 118-day grazing season.

2. Materials and methods

2.1. Study animals

The study design and procedures were approved by the testing facility Institutional Animal Care and Use Committee (approval code ZO1501). In May 2013, a total of 210 steers, approximately 6–8 months old and naturally infected with gastrointestinal nematodes, were obtained from pastures near Galt, California, USA. Steers were typical beef breeds for this region consisting of English and Continental crosses. The last prior anthelmintic treatment at the source location in California was injectable doramectin in November 2012. Prior anthelmintic treatments at the source site prior to November 2012 were not known, but the site had been used previously to graze cattle. For this study, the steers were transported to the research feedlot in southwest Idaho, USA. Three days (Day -17) following receipt, steers were processed, weighed, and sampled for fecal Strongylida egg count. At initial 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, Zoetis Inc.); *Clostridium chauvoei, Cl. septicum, Cl. haemolyticum, Cl. novyi, Cl. tetani*, and *Cl. perfringens* types C and D (Covexin® 8, Merck Animal Health); and *Moraxella bovis* (Piliguard® Pinkeye TriView®, Merck Animal Health). A total of 176 steers were selected for the study based on normal health and the highest fecal egg counts (average 226 eggs per gram of feces or EPG, range 5–1705 EPG). The selected steers weighed 310 kg on average with a range of 247 kg–385 kg. The remaining 34 steers with the lowest fecal egg counts were removed from the population. At 12 to 13 days after initial receipt (Days -8 to -7) selected animals were moved from dry lot confinement pens to irrigated pastures located at the same research facility. After five to six days on pasture (Day -2), steers were again weighed to determine body weights for dosing on Day 0. At all points during the study, cattle were weighed on a certified scale that was verified with certified weights prior to use. On Day 0 the steers were again individually weighed, sampled for fecal Strongylida egg count, and administered the assigned treatment.

2.2. Animal allocation and treatment groups

Following a generalized randomized block design with one-way treatment structure replicated across three pastures, the selected steers were blocked by pre-treatment body weights and paddock location within pasture with fecal egg counts being stratified within the weight blocks. Within a block, paddocks were randomly assigned to one of four treatments such that each block had at least one paddock per treatment group. Each paddock was randomly assigned four animals and the experimental unit was the individual paddock.

The four treatments were injectable doramectin (Dectomax®, Zoetis Inc., 0.2 mg kg^{-1}BW, SC), injectable doramectin plus oral albendazole (Valbazen®, Zoetis Inc., 10 mg kg^{-1}BW, PO), extended release injectable eprinomectin (LongRange™, Merial Limited, 1 mg kg^{-1}BW, SC) or saline. A total of 8 paddocks (32 animals) were assigned to the saline group while a total of 12 paddocks (48 animals) were assigned to each of the other treatment groups. Saline was injected subcutaneously at the same dose rate as doramectin and extended release injectable eprinomectin (1 mL/50 kg). All treatments were administered according to label directions and were dosed based on the individual body weight. Feed and water were not withheld prior to treatment. 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 2.5 mL increment. All treatments were administered by unmasked site personnel who played no role in data collection or animal evaluation.

2.3. Pastures and general animal health

A total of three irrigated pastures located at the research facility were utilized for the study. Pastures were immediately adjacent with similar forage and grazing history resulting in similar pasture parasite contamination. Prior anthelmintic use on the selected pastures had been primarily macrocyclic lactones administered once or twice per calendar year. Summer cattle grazing had occurred on the pastures for more than 30 years. Pastures were subdivided with electric fence into treatment paddocks containing four animals each, such that there were 18 paddocks in the first pasture, 15 in the second pasture, and 11 in the third pasture. Steers stayed on the same paddock for the entire 118-day grazing period. Pastures were flood irrigated approximately every 12–24 days. Pasture stocking rate was 0.99 head/ha. The stocking rate per ha was light enough to ensure forage would remain excellent during the main grazing season. To ensure steers were in the correct treatment paddock, color coded ear tags were used. Water was available *ad libitum* on one end of the paddock. During the study 28 animals were treated with antibiotic therapy for infectious conjunctivitis. Two animals were removed during the trial due to a chronic leg injury and failure to stay within the assigned pasture. For fly control, all steers were treated with a pour-on 5.0% permethrin product on Days 14, 60, and 90 (Boss® Pour-On, Merck Animal Health).