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The efficacy of eprinomectin extended-release injection against naturally acquired nematode parasites of cattle, with special regard to inhibited fourth-stage *Ostertagia* larvae

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ABSTRACT

The efficacy of eprinomectin in an extended-release injection (ERI) formulation in the treatment of cattle harboring naturally acquired nematode populations (including inhibited nematodes) was evaluated. Five studies were conducted under a similar protocol in the USA, the UK, and in Germany. All study animals were infected by grazing naturally contaminated pastures. The adequacy of pasture infectivity was confirmed by examining tracer calves prior to allocation and treatment of the study animals. The cattle were of various breeds or crosses, weighing 79–491 kg, and aged approximately 6–15 months. In each study, 20 animals were infected by grazing, and then removed from pasture and housed in a manner to preclude further nematode infections for 8–16 days until treatment. Animals were blocked based on descending pre-treatment body weight and randomly allocated to one of two treatments: ERI vehicle (control) at 1 mL/50 kg body weight or eprinomectin 5% (w/v) ERI at 1 mL/50 kg body weight (1.0 mg eprinomectin/kg). Treatments were administered once on Day 0 by subcutaneous injection in front of the shoulder. For parasite recovery and count, all study animals were humanely euthanized 14/15 days after treatment. Cattle treated with eprinomectin ERI had significantly ($p < 0.05$) fewer of the following nematodes than the controls with overall reduction of parasite counts of ≥94%: adult *Dictyocaulus viviparus, Capillaria* spp., *Cooperia oncophora*, *Cooperia pectinata*, *Cooperia punctata*, *Cooperia surnabada*, *Haemonchus placei*, *Nematodirus helvetianus*, *Oesophagostomum radiatum*, *Ostertagia lyrata*, *Ostertagia ostertagi*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Trichuris discolor*, *Trichuris skrjabini*, and *Trichuris* spp.; developing fourth-stage larvae of *Ostertagia* spp. and *Trichostrongylus* spp.; and inhibited fourth-stage larvae of *Cooperia* spp., *Haemonchus* spp., *Nematodirus* spp., *Oesophagostomum* spp., *Ostertagia* spp., and *Trichostrongylus* spp.

Animal treatments were well accepted, with no adverse reactions to treatment observed in any study animals. The results of this series of controlled studies demonstrated high therapeutic efficacy and acceptability of eprinomectin ERI against pulmonary nematodes and a wide range of gastrointestinal parasitic infections, including inhibited gastrointestinal nematodes, in cattle.

1. Introduction

Eprinomectin, a recently commercialized member of the macrocyclic lactone class of parasiticides has been proven highly effective as a pour-on formulation for

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cattle in the prevention and control of a wide range of endo- and ectoparasites in cattle (e.g., Barth et al., 1997; Shoop et al., 1996; Gogolewski et al., 1997a,b; Holste et al., 1997, 1998; Pitt et al., 1997; Williams et al., 1997; Yazwinski et al., 1997; Cramer et al., 2000; Campbell et al., 2001; Davey and George, 2002; Shoop and Soll, 2002; Rehbein et al., 2005). While highly effective as a pour-on formulation in providing persistent therapeutic control, prophylactic success also has been demonstrated against important nematode species (e.g., Batty et al., 1999; Epe et al., 1999; Dorny et al., 2000).

In a concerted effort to further lengthen the persistent activity of eprinomectin an extended-release injection (ERI) formulation has been developed for cattle which releases the active material in an efficacious manner for up to 150 days (Soll et al., 2013). This new formulation provides flexibility for strategic protection and control of endo- and ectoparasites.

The studies reported here were designed to confirm the efficacy and acceptability of eprinomectin ERI when administered to cattle harboring naturally acquired gastrointestinal and pulmonary nematode infections, including inhibited nematodes. Inhibition of development in the immature stage is a characteristic feature in the life-cycle of ruminant trichostrongyloid nematodes, occurring in *Cooperia, Haemonchus*, *Trichostrongylus*, *Nematodirus*, and *Ostertagia species*. However, inhibition is of special epidemiological and pathogenic relevance in *Ostertagia ostertagi*, the most economically important gastrointestinal nematode in cattle. The larval inhibition appears to be induced by environmental stimuli – climatic conditions less favorable for development and/or survival of free-living larval stages (fall of temperatures in autumn in northern temperate regions or dry and hot conditions in southern temperate climates) – but might also be affected by the development of both acquired immunity and age resistance. The duration of arrested development has been documented to last from a few weeks up to several months, so potentially large numbers of larvae can accumulate (Bürger, 1992; Taylor et al., 2007).

2. Materials and methods

Five controlled studies were conducted according to a similar protocol, three in the USA, one in the UK, and one in Germany. Cattle harboring naturally acquired nematode infections were utilized. The studies were designed and conducted to comply with the regulatory requirements of both the FDA/CVM and the European Medicines Agency/Committee for Medicinal Products for Veterinary Use, and according to relevant guidelines for Good Clinical Practices (GCPs) and for establishing the efficacy of cattle anthelmintics.

All five studies were performed in a blinded fashion, and personnel involved with data collection were unaware of the treatment group assignments.

2.1. Experimental animals

A total of 100 (42 male, 35 male castrate, 23 female) healthy, ruminating Angus cross, other beef crossbreds, Holstein, Holstein Friesian, and Friesian cattle, weighing 79–491 kg prior to treatment (Days −1 or 0), and aged approximately 6–15 months at the time of treatment were used. The five studies were conducted in the USA (Study #2 in Arkansas during June, #4 in Louisiana during May, and #5 in Missouri during September to December), in Germany (Study #3 in Upper Bavaria during December), and in the UK (Study #1 in Scotland during November to December). The animal descriptions and details are presented in Table 1. None of the animals had been previously treated with an avermectin or milbemycin product.

Cattle for all five studies were grazed on naturally contaminated pastures prior to treatment and were expected to be harboring naturally acquired nematode infections. To confirm pasture infectivity and to demonstrate the presence of adequate nematode infections (including inhibited fourth-stage larvae), a total of 16 tracer animals (at least two animals per study site) were commingled with the study animals. They were removed from pasture, housed to preclude further nematode infection, and were necropsied 8–16 days later for parasite identification and enumeration. Examination of tracer calves was completed prior to Day 0 for animals enrolled in the efficacy studies.

2.2. Study design

Each of the studies was conducted utilizing a randomized block design. Ten replicates of two animals each were formed based on descending Day −1 or Day 0 body weights. Within replicates, one animal was randomly allocated to each treatment group. Group 1 animals received the ERI vehicle (control) at 1 mL/50 kg bodyweight subcutaneously once on Day 0. Group 2 animals received eprinomectin 5% (w/v) ERI solution at a targeted dosage of 1.0 mg eprinomectin/kg bodyweight (1 mL/50 kg) subcutaneously once on Day 0. The appropriate dose volume for each animal was administered in front of the right or left shoulder using commercial syringes and needles. Dose volumes were based on pre-treatment body weights and measured at 0.1 mL increments. Calculated doses that fell between increments were rounded up to the next greater 0.1 mL.

2.3. Parasite counts

All study animals were humanely euthanized and necropsied for nematode counting and identification 14/15 days after treatment (22–31 days after removal from pasture). The following organs were removed for content recovery and examination: heart–lung complex (Studies 4 and 5), lungs with trachea (Studies 2 and 3), abomasa, small intestines and large intestines (including the cecum, all studies). Total lungworms were collected and counted. The contents of the abomasa, small intestines and large intestines were collected separately and diluted with water. The abomasum and small intestine of each calf were incubated separately (saline soak) to recover mucosal stages of the parasites for counting and identification. For all animals within each study, the entire contents or a known percentage of the contents of each organ (abomasum and small intestine contents: 2.5%, 5%, 10% or 20%