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Nematode burdens of pastured cattle treated once at turnout with eprinomectin extended-release injection

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ABSTRACT

The efficacy of eprinomectin in an extended-release injection (ERI) formulation was evaluated against infections with third-stage larvae or eggs of gastrointestinal and pulmonary nematodes in cattle under 120-day natural challenge conditions in a series of five studies conducted in the USA (three studies) and in Europe (two studies). For each study, 30 nematode-free (four studies) or 30 cattle harboring naturally acquired nematode infections (one study) were included. The cattle were of various breeds or crosses, weighed 107.5–273 kg prior to treatment and aged approximately 4–11 months. For each study, animals were blocked based on pre-treatment bodyweight and then randomly allocated to treatment: ERI vehicle (control) at 1 mL/50 kg bodyweight or Eprinomectin 5% (w/v) ERI at 1 mL/50 kg bodyweight (1.0 mg eprinomectin/kg) for a total of 15 and 15 animals in each group. Treatments were administered once on Day 0 by subcutaneous injection in front of the shoulder. In each study, all animals grazed one naturally contaminated pasture for 120 days. At regular intervals during the studies, fecal samples from all cattle were examined for nematode egg and larval counts. In four studies pairs of tracer cattle were used to monitor pasture infectivity at 28-day intervals before and/or during the grazing period. All calves were weighed before turnout onto pasture and at regular intervals until housing on Day 120. For parasite recovery, all study animals were humanely euthanized 27–30 days after removal from pasture.

Cattle treated with Eprinomectin ERI had significantly ($p < 0.05$) fewer strongylid eggs ($\leq$1 egg per gram; egg count reduction $\geq$ 94%) than the control cattle and zero lungworm larvae at each post-treatment time point. At euthanasia, cattle treated with Eprinomectin ERI had significantly ($p < 0.05$) fewer of the following nematodes than the ERI vehicle-treated (control) cattle with overall reduction of nematode counts by >92%: *Dictyocaulus viviparus* (adults and fourth-stage larvae (L4), *Bunostomum phlebotomum*, *Cooperia curticei*, *Cooperia oncophora*, *Cooperia punctata*, *Cooperia surnabada*, *Cooperia* spp. inhibited L4, *Haemonchus contortus*, *Haemonchus placei*, *Haemonchus* spp. inhibited L4, *Nematodirus helvetianus*, *Nematodirus* spp. inhibited L4, *Oesophagostomum radiatum*, *Oesophagostomum* spp. inhibited L4, *Ostertagia leptospicularis*, *Ostertagia lyrata*, *Ostertagia ostertagi*, *Ostertagia* spp. inhibited L4, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Trichostrongylus*

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spp. inhibited L4, *Trichuris discolor*, and *Trichuris ovis*. Over the 120-day grazing period, Eprinomectin ERI-treated cattle gained between 4.8 kg and 31 kg more weight than the controls. This weight gain advantage was significant ($p < 0.05$) in three studies.
All animals accepted the treatment well. No adverse reaction to treatment was observed in any animal in any study.

1. Introduction

Collectively, gastrointestinal nematodes and lungworms are still considered the most commonly occurring and most economically important parasites of grazing cattle in temperate regions worldwide.

Although parasitic infections in the majority of the cattle are often subclinical in current management systems where antiparasitics are used for prophylactic control, infection with those parasites can cause severe parasitic gastroenteritis and parasitic bronchitis, especially in young stock which are most susceptible in their first grazing season. Knowledge of the epidemiology of parasitic nematodes has led to the creation of parasite control programs which aim to suppress the fecal egg output of grazing cattle by the use of early season anthelmintic prophylaxis and thus reduce the accumulation of infective larvae in the environment later in the season. The repeated strategic (prophylactic) administration of anthelmintics has proven to be highly effective in the prevention of clinical disease and/or production losses. The superior efficacy and extended duration of activity of the macrocyclic lactones in injectable and pour-on formulations led to an important extension of the intervals between treatments in these programs. High labor and equipment costs resulting from frequent gathering of cattle for treatment administration resulted in the development of various forms of intraruminal boli (controlled-release devices) that were formulated for delivery of anthelmintics for up to 4 months following a single administration, either by continuous low-level release or by pulse-release of the drug.

The endectocidal effectiveness of eprinomectin, the most recent commercialized member of the macrocyclic lactone class of parasiticides as used in a 0.5% pour-on formulation at 0.5 mg eprinomectin/kg bodyweight, has been extensively documented (Barth et al., 1997; Gogolewski et al., 1997a,b; Holste et al., 1997, 1998; Pitt et al., 1997; Williams et al., 1997; Yazwinski et al., 1997; Campbell et al., 2001; Davey and George, 2002; Rehbein et al., 2005). Dose titration studies have demonstrated eprinomectin represents a threefold greater potency against ruminant gastrointestinal nematodes than ivermectin (Shoop et al., 1996; Shoop and Soll, 2002). The commercialized eprinomectin pour-on formulation has considerable persistent activity against a range of important nematodes (Cramer et al., 2000; Holste et al., 2002) and has been used successfully in prophylactic treatment programmes (Batty et al., 1999; Epe et al., 1999; Dorny et al., 2000).

In order to extend the persistency of activity of eprinomectin against endoparasites, an injectable formulation has been developed which is not only effective in removing existing nematode infections (Hunter et al., 2013; Rehbein et al., 2013) but also releases the active ingredient in concentrations to provide effective control of nematode infections in cattle for up to 150 days after treatment as demonstrated in single point challenge studies (Soll et al., 2013). In this extended-release formulation, eprinomectin is released from a matrix formed with poly(D,L-lactide-*co*-glycolic)acid (PLGA). PLGA is known as a safe and effective biodegradable material which has been used as a drug delivery system for extended release applications of various pharmaceutical compounds including ivermectin (Lewis, 1990; Miller et al., 1999; Clark et al., 2004; Winzenburg et al., 2004).

The studies reported here were designed to confirm the efficacy of eprinomectin extended-release injection (ERI) over the entire duration of activity of the product, i.e., nematode-free or naturally infected calves received a single injection of eprinomectin ERI at turnout and were subsequently and continuously exposed to nematode challenge by grazing permanent pasture for 120 days.

2. Materials and methods

A total of five controlled studies were conducted according to similar protocols, three in the USA and one each in Germany and in the UK. In four studies (Studies 1–4), nematode-free calves were used, while one study utilized calves harboring naturally acquired nematode infections (Study 5). 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.

The studies were performed as blinded studies, i.e., all personnel involved in collecting data were masked to the treatment assignment of the animals.

2.1. Experimental animals

A total of 150 (67 male castrate, 83 female) healthy, ruminating Holstein, Limousin, Pinzgauer and cross-bred beef cattle, weighing 107.5–273 kg prior to treatment (Days −3, −1 or 0), and aged approximately 4–11 months were included in five studies conducted in the USA (Studies 3, 4, and 5 – Arkansas, Idaho, Missouri), in Germany (Study 2, Upper Bavaria), and in the UK (Study 1, Hertfordshire). The animal descriptions and details are presented in Table 1. Animals had not been previously treated with an avermectin or milbemycin product.

Animals enrolled in Studies 1–4 were worm-free (as determined by fecal examination prior to study start, i.e., Days −15 or −14), with the exception of one animal in