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Gastrointestinal parasitism reduces the plasma availability of doramectin in lambs

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Abstract

A study was undertaken to investigate the effect of parasitism on plasma availability and pharmacokinetic behaviour of doramectin (DRM) in lambs. Fourteen parasitised grey face Suffolk lambs (26.9 ± 1.5 kg bodyweight) were selected for the study. Seven pairs of lambs were allocated to two groups to obtain an approximately even weight distribution. Group I (non-parasitised) was pre-treated with three repeated administrations of 5 mg/kg fenbendazole to maintain a parasite free condition. In group II (parasitised), the lambs did not receive any anthelmintic treatment. After the 85-day pre-treatment period, both groups of animals were treated with DRM by subcutaneous (SC) injection in the shoulder area at 200 μg/kg. Throughout the experimental period, both groups were maintained together under similar feeding and management conditions. Blood samples were collected by jugular venepuncture at different set times between 0.5 h and 60 days post-treatment. After plasma extraction and derivatisation, samples were analysed by high performance liquid chromatography (HPLC) with fluorescence detection. A computerised kinetic analysis was performed and the data were compared using the Student's paired *t* test.

The parent molecule was detected in plasma between 30 min and either day 20 (parasitised) or day 35 (non-parasitised) post-DRM treatment. The AUC values of the parasitised group (143.0 ± 18 ng d/mL) were significantly lower ($P < 0.05$) than those observed in the parasitically naïve animals (229.6 ± 21.7 ng d/mL). The mean residence time (MRT) in the parasitised group (3.4 ± 0.3 days) was significantly shorter ($P < 0.05$) than in the healthy group (6.6 ± 0.6 days). Study results have shown that parasitic disease, through alteration in the body condition, can produce significant changes in the plasma disposition of DRM when administered SC to parasitised lambs.

Keywords: Doramectin; Pharmacokinetics; Anthelmintics; Parasitised lambs

1. Introduction

Verminous gastroenteritis is an endoparasitosis that principally affects young ruminant animals by reducing their ability to absorb and efficiently utilise nutrients causing anorexia and weight loss (Garriz et al., 1987). Nematode infections are a major cause of economic loss in ruminants throughout the world (Holmes, 1987) and the administration of anthelmintics is the most common method used by farmers to control endoparasites. Recent developments for use in cattle include various forms of slow-release boluses and dermal and injectable preparations, although oral drenches are still used to treat a large percentage of cattle and are still almost exclusively used in sheep (Taylor et al., 1992). Chemotherapy continues to serve as the cornerstone of parasite control, but anti-parasitic compounds constitute a

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limited resource and their future will be impacted by a variety of factors including the development of parasite resistance.

Macrocyclic lactones, commonly referred to as endectocides, have been used to treat parasitism in livestock for almost two decades. During this period, there has been significant improvement in their chemistry resulting in increasing potency and duration of action. The combination of low dose rate, convenient formulation, high potency, unique biochemical action and pharmacokinetic behaviour, all conductive to prolonged availability in the parasitised animal, make macrocyclic lactone endectocides a very attractive "*drug of choice*" (Hennessy, 1999).

Doramectin is a broad-spectrum macrocyclic lactone endectocide belonging to the avermectin class family of compounds. In ewes, the injectable doramectin solution is indicated for the treatment and control of several species of gastrointestinal roundworms, lungworms, eyeworms, sucking lice and mange mites following a subcutaneous (SC) or intramuscular (IM) administration of 200 μg/kg (Taylor, 1999; Dorchies et al., 2001; Simon and Fergusson, 2004). The persistent anti-parasitic efficacy of doramectin has been attributed to the combination of inherent potency and an extended plasma pharmacokinetic profile (Owens and Schneider, 2000).

Anthelmintics are thoroughly tested before licensing, and consequently their pharmacokinetic behaviour, plasma concentrations after administration of therapeutic doses and tissue residues are known. Most pharmacokinetic experiments are performed on housed animals that are fed hay and, if necessary, a small additional concentrate ration, to facilitate the frequent blood sampling required. The pharmacokinetic data obtained are assumed to indicate what will happen with the same dose under field conditions, where most parasitological trials take place (Taylor et al., 1992). However, parasitism, through the changes induced in the nutritional status of host animals, may induce changes in adipose tissue deposition and in body fluid dynamics. Such changes are likely to affect the distribution pattern, plasma protein binding, and the efficacy of anthelmintic compounds (Lanusse and Prichard, 1993).

Pharmacodynamics may be thought of as the nexus of efficacy and pharmacokinetics. Attaining a therapeutic effect requires that a drug be in the right place for an adequate time and in a sufficient concentration to exert the desired response (Geary et al., 1999). There is evidence that changes in the pharmacokinetic behaviour and metabolism of anthelmintics may result in reduced clinical efficacy and facilitate selection for resistant strains. The understanding of factors affecting the pharmacology of anthelmintics in animal production is crucial for parasitic control optimisation (Lanusse and Prichard, 1993).

Like other avermectins, doramectin disposition is due to its high lipophilicity characterised by a long residence time and large distribution volume due to drug accumulation in fat and other tissues. The aim of the present study was to elucidate the effect of gastrointestinal parasitism on the pharmacokinetic behaviour of doramectin when administered SC to lambs.

2. Materials and methods

Fourteen grey-face Suffolk lambs, aged between 3 and 4 months and 26.9 ± 1.5 kg bodyweight, were selected for the study. During the experimental period the lambs were maintained together, outdoors during the day and housed at night. They were fed daily with a rye grass and clover hay mix and a supplementary concentrate. Water and hay were provided ad libitum. They also had access to a paddock with a natural grass pasture. All lambs were weighed before the treatments by a digital scale. A serum clinical biochemistry panel including hepatic function tests was performed to evaluate the animals' health, and all values were within the normal ranges described for the ovine species under basal conditions (Meyer et al., 1992).

To identify the natural infection level, faecal examinations were performed on all lambs to determine faecal egg counts (FEC). Quantitative pre- and post-treatment FEC were performed using a modified McMaster technique (Zajac, 1994) during a 90-day period prior to and a 70-day period after ivermectin treatment. All faecal samples were obtained from the rectum during the 7-day interval between the two periods. A minimum of 200 eggs per gram (epg) of faeces was established for lamb incorporation into the experimental groups.

Seven pairs of lambs were allocated into two groups equally balanced by body weight and sex. Once the animal pairs were established, their distribution to the experimental groups was performed according to nematode faecal egg count so as to place animals with higher values in the parasitised group. In group I, the animals were treated three times with an oral (PO) administration of 5 mg/kg fenbendazole (Panacur, Intervet) in order to maintain a healthy, parasite-free condition for an 85-day period. As well as good efficacy with the main gastrointestinal sheep nematodes, fenbendazole was selected due to its faster elimination rate and short persistence of their active metabolite concentrations in plasma after oral administration in sheep (Lanusse et al., 1995). Considering these characteristics, we assumed that fenbendazole would not produce any effect on the pharmacokinetics of doramectin. In group II (parasitised), infection was sustained by oral inoculation with nematode cultures in the infective stage. A mixed larval inoculum containing approximately 5000 third-stage strongyle larvae (40% *Ostertagia*, 28% *Trichostrongylus*