THE ROLE OF ABSORBED DRUG IN THE EFFICACY OF OXFENDAZOLE AGAINST GASTROINTESTINAL NEMATODES

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ABSTRACT


Comparisons were made of the relative efficacy of oxfendazole (OFZ), administered to sheep at 5 mg/kg either as an oral drench, single intravenous injection or 12 and 24 divided intravenous injections over 24 and 48 hours, against benzimidazole-resistant Haemonchus contortus and Trichostrongylus colubriformis. A single intravenous injection was at least equally potent as the oral drench whilst the divided dose intravenous regimes significantly increased OFZ efficacy against both parasite species.

These findings demonstrate that (i) absorbed drug is important for the efficacy of OFZ against nematodes in the abomasum and small intestine and may be more important than unabsorbed drug passing down the gastrointestinal tract, and (ii) the maintenance of plasma OFZ levels of approximately 2 μg/ml by divided dose regime increased efficacy compared with that achieved with the same total dose given as a single administration.

INTRODUCTION

In a previous report Prichard et al. (1978) demonstrated that the efficacy of benzimidazole anthelmintics is related to the duration of exposure of the worm to the drug. A rapidly absorbed, metabolised and excreted drug such as thiabendazole (TBZ) is anthelmintically less potent against resistant worms than are more slowly metabolised and excreted benzimidazoles (Prichard, 1978).

Following oral administration to ruminants, the rumen acts as a drug reservoir from which plasma concentrations of some anthelmintics can be sustained for a period. To simulate the pharmacokinetic behaviour of an anthelmintic being slowly absorbed from the rumen, Prichard et al. (1978) infused TBZ into the rumen of cattle, with natural infections of arrested Ostertagia ostertagi, over a period of 36 hours. This prolonged administration
maintained circulating plasma TBZ levels and caused more than 90% of these normally TBZ-tolerant larvae (Armour, 1969) to be removed. It appeared, therefore, that a prolonged plasma half-life of benzimidazole (BZ) anthelmintics might be a major factor in drug potency.

However, plasma concentrations may only reflect drug levels in the organs of the host. It was uncertain which was more important for the activity of benzimidazoles against gastrointestinal parasites, the drug passing down the gastrointestinal tract or the absorbed drug circulating in the bloodstream. In an attempt to clarify this uncertainty, ozfendazole (OFZ) was administered both orally and intravenously to infected sheep and the resultant anthelmintic efficacy assessed. In addition, it was decided to determine whether the maintenance of moderately high plasma drug concentrations over one or two days would increase efficacy. Thus, some sheep were given divided doses intravenously every 2 hours over 24 or 48 hours. The efficacy achieved by the various administration regimes was determined using BZ-resistant worms against which the normal oral dose is only moderately or poorly effective. The purpose of this was to allow shifts in efficacy, both increases and decreases, to be detected, whereas if highly susceptible worms were used there would be little possibility for determining shifts in efficacy.

MATERIALS AND METHODS

Thirty worm-free 9-month-old Border Leicester x Merino crossbred sheep were infected per os with 5,000 BZ-resistant Haemonchus contortus (VRSG H.c. selected strain, Glenfield) and 10,000 Trichostrongylus colubriformis (VRSG CPS strain, Glenfield). The sheep were maintained in concrete pens which were cleaned daily and fed a stock ration of 1:1 lucerne/wheaten hay, and water ad libitum. On day 21 the sheep were ranked in order of faecal egg count and allocated to 6 egg count classes, each of 5 sheep. One sheep from each of these classes was randomly allocated to one of 5 groups of 6 sheep.

The 5 groups of sheep were treated on day 22 post-infection as follows:

Group 1: control

Group 2: oral administration of OFZ, 5 mg/kg (Systamex, Batch No. 8D346 Australia)

Group 3: intravenous administration of 5 mg pure OFZ/kg in solution

Group 4: intravenous administration of 5 mg OFZ/kg given as 0.417 mg pure OFZ/kg in solution at 2-hourly intervals over a period of 24 hours

Group 5: intravenous administration of 5 mg OFZ/kg given as 0.208 pure OFZ/kg in solution at 2-hourly intervals over a period of 48 hours.

Twenty-four hours prior to treatment the sheep in Groups 4 and 5 were fitted with a jugular catheter for drug administration and transferred to metabolism.