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Further characterisation of a triple resistant field isolate of *Teladorsagia* from a Scottish lowland sheep farm

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Abstract

Anthelmintic efficacies against juvenile developing populations of *Teladorsagia* species that were known to be resistant to anthelmintics from all three broad spectrum families were examined using a controlled efficacy test. Fenbendazole (FBZ), levamisole (LEV), ivermectin (IVM), combinations of these anthelmintics and moxidectin (MOX) were assessed in parasite naïve lambs artificially infected with 8000 third stage larvae (Tci5) and treated orally 8-day post-infection with the compounds at the manufacturers recommended dose rates, FBZ, 5 mg/kg body weight (BW); LEV, 7.5 mg/kg BW; IVM, 0.2 mg/kg BW; MOX (0.2 mg/kg BW). The lambs were slaughtered 14-day post-treatment. The arithmetic mean worm burden reductions resulting from oral treatments with FBZ; IVM; LEV; FBZ + IVM; FBZ + LEV; FBZ, LEV + IVM or MOX were 36%, 82%, 38%, 86%, 60%, 88% and 97%, respectively. The results illustrate that combination treatments showed improved efficacies against the juvenile population compared to individually administered treatments but that these improvements were not wholly effective. Moxidectin was the only treatment that was over 95% effective, though caution should be noted when advising the use of MOX prophylactically since 3% of the infection still survived this treatment. Treatments directed at juvenile stages of Tci5 were less effective, with the exception of IVM, compared to a similar trial using Tci5 where the same treatments were directed against a predominantly adult population. No interaction was detected comparing the timings of treatments and its effectiveness with the exception of IVM (two-way ANOVA, $p < 0.05$). These findings suggest that, on the whole, the selection processes for anthelmintic resistance (AR) may occur at an early stage of development within the parasites, having severe implications for the early detection of AR.

Keywords: Anthelmintics; Assay; Benzimidazole; Efficacy; In vivo; Ivermectin; Levamisole; Moxidectin; Resistance; *Teladorsagia circumcincta*

1. Introduction

To date therapeutic treatments administered against nematodes resistant to more than one drug class has relied either on switching to the anthelmintic class that

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the nematode is not resistant to or the use of combination therapies (McKenna et al., 1996). The selection of multiple resistant nematode populations that can survive treatments with drugs within the three broad spectrum families reduces the options for therapeutic treatments to combinations or drugs within the families that have still retained some useful activity. *Teladorsagia* species resistant to all three drug groups have been reported within sheep flocks from Great Britain over the last 5 years (Sargison et al., 2001; Yue et al., 2003; Bartley et al., 2004). In a previous controlled efficacy test (CET; Bartley et al., 2004) individually administered doses of fenbendazole (FBZ), levamisole (LEV), ivermectin (IVM) and combinations of these anthelmintics or moxidectin (MOX) were tested against predominantly adult infections (day 28 post-infection, PI). In that study the respective overall efficacies for FBZ; IVM; LEV; FBZ + IVM; FBZ + LEV; FBZ, LEV + IVM or MOX were 59%, 60%, 88%, 94%, 93%, 92% and 98%. However, in that study there were also small numbers of immature worms recovered at post-mortem with some apparent reduction in efficacy against these immature stages (67%, 82% and 13% for FBZ, LEV and IVM). Since any stage specific differences in the expression of resistance might be important both with regard to therapeutic treatments and also might influence the processes of selection and transmission of resistance the aim of the current study was to examine the efficacy of the same treatments administered against immature stages (L_4, day eight PI).

2. Materials and methods

Forty six-month-old Suffolk greyface cross parasite naïve lambs were challenged with 8000 infective larvae of *Teladorsagia* species, predominantly *Teladorsagia circumcincta*, (Tci5). Since its recovery from the field the isolate, (Tci5) had been passaged four times in lambs but had not been exposed to any anthelmintic pressure. The lambs were weighed, divided into eight groups of five and dosed orally by syringe, in the manner described by Bartley et al. (2004), at the manufacturers recommended dose rate with either FBZ (Panacur®, 5 mg/kg body weight (BW)), LEV (Levacide®, 7.5 mg/kg BW), IVM (Oramec®, 0.2 mg/kg BW), MOX (Cydectin®, 0.2 mg/kg BW) singly or with combinations of FBZ and LEV (5 mg/kg and 7.5 mg/kg BW, respectively), FBZ and IVM (5 mg/kg and 0.2 mg/kg BW, respectively) or FBZ, LEV and IVM (5 mg/kg, 7.5 mg/kg and 0.2 mg/kg BW, respectively) 8-day post-infection or left untreated. Combination treatments were administered sequentially within a minute of each other: the treatments were not mixed prior to being administered to the lambs (Table 1).

2.1. Necropsy and worm recovery

All of the animals were necropsied 14-day post-treatment (22-day PI) using the post-mortem and worm recovery methods described by Patterson et al. (1996). The total worm burdens were estimated from separate 2% sub-samples of the abomasal washings

Table 1
Trial designs for the controlled efficacy tests, including dosage of anthelmintic, number of lambs on trial per group, infective dose, days post-infection of treatment and necropsy (PM)

Treatment (dosage)	Number of lambs	Dose (L_3)	Day post-infection	
			Treat	PM
Control-untreated	5	8000	–	22
Fenbendazole (5 mg/kg; FBZ)[a]	5	8000	8	22
Levamisole (7.5 mg/kg; LEV)[a]	5	8000	8	22
Ivermectin (0.2 mg/kg; IVM)[a]	5	8000	8	22
Moxidectin (0.2 mg/kg, MOX)[a]	5	8000	8	22
FBZ[a] + LEV[a]	5	8000	8	22
FBZ[a] + IVM[a]	5	8000	8	22
FBZ[a] + LEV[a] + IVM[a]	5	8000	8	22

[a] Anthelmintics when used alone or as part of a combination were administered at manufacturers recommended dose rate for sheep.