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Short communication

Cross-resistance to moxidectin and ivermectin on a meat sheep farm in France

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ABSTRACT

Resistance to ivermectin and moxidectin was explored by a faecal egg count reduction test in two sheep flocks with suspected anthelmintic resistance. The FECRT confirmed one suspicion, with a mean percentage of reduction in egg excretion within the treated groups of 0% for ivermectin (CI 95%: −228 to 58) and 13% for moxidectin (CI 95%: −152 to 70). This was further explored by a controlled efficacy test. An experimental infection of 18 naïve lambs was set up using infective larvae isolated from this flock (5000 L3/lamb). Compared to the control group, abomasal worm burdens (*Teladorsagia circumcincta*) were reduced by 90% [CI 95%: 81.5–94.8] and 85% [CI 95%: 72.4–92.2] after ivermectin ($p < 0.05$) and moxidectin ($p < 0.05$) treatment respectively. Again, compared to the control group, there was a reduction for intestinal strongyles (*Trichostrongylus colubriformis*) of 100% and 99% [CI 95%: 97.5–99.7] for ivermectin and moxidectin respectively. No difference was found between the efficacy of moxidectin and ivermectin. Pharmacokinetic values indicated that the strongyles were submitted to anthelmintic concentrations usually lethal to them. This trial demonstrated the first multiple resistance of ovine strongyles in France.
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1. Introduction

Anthelmintic resistance in small ruminant strongyles has been known for several years. A recent review reported that anthelmintic resistance is widespread among European farmed ruminants (Rose et al., 2015). The three main species infecting sheep (*Haemonchus contortus*, *Teladorsagia circumcincta* and *Trichostrongylus colubriformis*) and all the anthelmintic families are concerned.

In this study, we explored two field suspicions of resistance to ivermectin and moxidectin by a faecal egg count reduction test (FECRT), which is the standard field test for the diagnosis of anthelmintic resistance in small ruminants (Coles et al., 2006). In one case, this was followed by a controlled efficacy test comprising pharmacokinetic analysis of the two anthelmintics.

2. Materials and methods

2.1. FECRT

The first flock was a meat sheep flock situated in the Loire *département* (a *département* being a French administrative and territorial unit) comprising 420 Ile de France ewes. The ewes graze from April to November with a density of ten ewes/ha and a small degree of pasture rotation. They are treated by oral moxidectin (MOX) in June and November and with injectable MOX or ivermectin (IVM) when they come back from summer pastures. Lambs are treated with oral MOX every 35 days. Rams are not treated at the time of integration in the flock.

The second meat sheep flock was situated in the Allier department and comprised 700 Ile de France ewes. The ewes graze all year round, without any pasture rotation. They were treated four times a year with levamisole and oxfendazole alternately until 2003 then levamisole-IVM from 2003 to 2006 and from then onwards with levamisole-MOX alternately. Lambs were treated at 30 days old with benzimidazoles and at 60 days old with levamisole until

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2003 then with MOX until now. Since 2009, the rams have been given MOX when integrated in the flock.

In each flock, FECRT was conducted according to the recommendations of the World Association for the Advancement of Veterinary Parasitology (WAAVP) (Coles et al., 2006). Three groups of 15 lambs per flock were randomly constituted:

- Control group: 15 lambs were left untreated,
- IVM group: 15 lambs were given 0.2 mg/kg bodyweight (BW) of IVM orally (Oramec®, Mérial, France),
- MOX group: 15 lambs were given 0.2 mg/kg BW of MOX orally (Cydectine®, Zoetis, France).

All the lambs were weighed and treated with the exact dose. Individual faecal samples were collected before and 16 days after treatment.

Individual faecal egg counts were completed using a modified McMaster technique (flotation solution: magnesium sulphate (d = 1.25), sensitivity: 50 eggs per gram of faeces (epg)) (Raynaud, 1970). The remaining faeces were pooled to perform group coprocultures performed separately for control and treated groups. Infective larvae were harvested by the Baermann technique and identified to genera level (MAFF, 1986).

For each group and time, mean epg was calculated using a binomial negative regression (epg being the response variable, and group and date the explanatory variables).

The percentage of reduction was estimated using the estimated means in the Presidente formula (Presidente, 1985): $FECR = 100 \times (1 - [T2/T1][C1/C2])$ where T1 and T2 were pre- and post-treatment geometric means of the epg in treated groups respectively, and C1 and C2 were pre- and post-treatment geometric means of the epg in control groups respectively.

Confidence intervals were calculated using a non-linear combination of estimators in Stata (StataCorp).

Results were interpreted according to WAAVP guidelines (Coles et al., 1992).

2.2. Controlled efficacy test

In the event of a suspicion of resistance following FECRT, a controlled efficacy test was performed.

Eighteen two-month-old naïve lambs which had never grazed were bought from a commercial flock. Infective larvae were obtained from bulk coprocultures from the flock in which resistance was suspected and each lamb was infected with 5000 L3.

When all the lambs were excreting eggs (35 days post-infection), they were divided up into three groups of six, so that mean egg excretion and mean weights were identical:

- Control group: six lambs were left untreated,
- IVM group: six lambs were given 0.2mg/kg BW of IVM orally (Oramec®)
- MOX group: six lambs were given 0.2mg/kg BW of MOX orally (Cydectine®).

The pharmacokinetics of IVM and MOX were determined: the plasma concentration of IVM and MOX was measured before administration of IVM or MOX and 1, 2, 4, 7 and 8 days post-administration by high-performance liquid chromatography (HPLC) using a previously described method (Lespine, 2004).

All the lambs were euthanised ten days after treatment and examined post-mortem. The abomasum and small intestines (the first three metres) were processed as described by MAFF (1986). Worm counts were conducted on aliquots of one tenth of the washing volume of the contents (500 ml). Worms present in the large intestines were sampled directly during post-mortem examination. Species were identified by examining 30 male worms, if available, from each organ.

The trials were carried out in compliance with animal welfare requirements and did not cause any pain according to French regulations on experiment ethics.

Worm burdens in the treated and untreated control group were compared using a Mann-Whitney test, with significance accepted at $p < 0.05$.

Data were analysed using a negative binomial regression. The efficacy of treatment was calculated for each organ and for the whole digestive tract and determined using the formula $([C–T]/C) \times 100$, where C is the mean adult worm count for the untreated control group and T is the mean adult worm count for each of the treated groups as described by Mejía et al. (2003). The confidence intervals for adult reduction were calculated by non-linear combination of the negative binomial regression estimates.

Pharmacokinetic parameters of IVM and MOX were compared using a Student test, with significance accepted at $p < 0.05$.

3. Results

3.1. FECRT

3.1.1. Flock 1

The trial took place in June 2013. The lambs were one year old, had been at grass the previous autumn, were naturally infected with nematodes and had a mean weight of 64 kg.

In the control group, the mean egg excretion of gastro-intestinal strongyles was 350 epg at J0 and 118 epg at J16 (Table 1). The mean percentage of the reduction in egg excretion in the treated groups compared to the control group was 0% for IVM (CI 95%: −228 −58)and 13% for MOX (CI 95%: −152 −70) (Table 1).

Coprocultures from the control group showed the presence of larvae mainly from the *Teladorsagia*/*Trichostrongylus* genera, followed by larvae from the *Oesophagostomum*/*Chabertia* genera. After treatment by IVM or MOX, only *Teladorsagia*/*Trichostrongylus* larvae were identified.

According to WAAVP recommendations, the FECRT indicated the presence of IVM and MOX resistance in the flock's strongyle population.

3.1.2. Flock 2

This trial took place in September 2013. The lambs were six months old, had been grazing since birth, were naturally infected with nematodes and had a mean weight of 44.7 kg.

In the control group, the mean egg excretion of gastro-intestinal strongyles was 213 epg at J0 and 313 epg at J16 (Table 1). The mean percentage of the reduction in egg excretion in the treated group compared to the control group was 96% for IVM (CI 95%: 85 – 99) and 98% for MOX (CI 95%: 86–100) (Table 1).

Coprocultures from the control group showed the presence of larvae mainly from the *Teladorsagia*/*Trichostrongylus* genera and secondarily the *Oesophagostomum*/*Chabertia* genera. After treatment, infective larvae were only obtained in the IVM group and were identified as *Teladorsagia*/*Trichostrongylus* larvae.

According to WAAVP recommendations, the FECRT indicated only a reduced efficacy of IVM and MOX in this flock's strongyle population.

3.2. Controlled efficacy test with the infective larvae from flock 1

All the lambs were free from infection before experimental infection. An anthelmintic treatment was administered 35 days post-infection, when all the lambs were excreting strongyle eggs.

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