Communication

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Lack of Efficacy of Albenzole against *Dicrocoelium dendriticum* Infection in a Sheep Farm in France

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Simple Summary: Infection by the parasite *Dicrocoelium dendriticum* has an impact on the production and health of sheep. As the parasite cycle is complex, management is based on antiparasitic treatment. Abendazole at a dose of 15 mg/kg is known to be effective against the adult stages of *Dicrocoelium dendriticum.* Following a suspected lack of efficacy of this treatment in a French sheep farm, we carried out an efficacy test by treating 15 ewes at a dose of 15 mg/kg. We obtained a treatment efficacy of 38%, well below the 90% efficacy or more observed in other studies with the same compound at the same dosage. This lack of efficacy of albendazole on this farm is a warning for sheep farms, as there are no other active molecules against *Dicrocoelium dendriticum* currently available in France.

Abstract: Dicrocoeliosis is a common parasitic disease in European sheep farming. The prevalence of infection by this parasite can reach almost 70% in areas where the environment is favourable to intermediate hosts. In France, only one drug is currently available for the treatment of dicrocoeliosis, albendazole at a dose of 15 mg/kg in a single administration. However, a control coproscopy following a routine treatment led us to suspect that the efficacy of albendazole against *Dicrocoelium dendriticum* had diminished. We therefore carried out an efficacy test on 15 animals by treating them with albendazole at a dose of 15 mg/kg and performing a coproscopy on D0 and a control coproscopy 14 days later. We obtained a 38% reduction in the excretion of *Dicrocoelium dendriticum* eggs. This shows a reduction in the expected efficacy of albendazole, which is normally more than 90% in other studies involving this molecule at a dosage of 15 mg/kg.

Keywords: *Dicrocoelium dendriticum*; albendazole; lack of efficacy

1. Introduction

Dicrocœliosis linked to the parasite *Dicrocœlium dendriticum* is a common parasitic disease of ruminants in Europe. A study by Cringoli et al showed a prevalence of infection of 67.5% in sheep during a study in the southern Italian Apenines [1], while in Sardaigne, it was 51.1% [2]. Similarly, a study carried out in the province of Leon, in north-west Spain, showed a prevalence of 63.6% in sheep [3]. These various studies show that *Dicrocœlium* is a parasite frequently found in these regions of southern Europe.

Dicrocœlium dendriticum is a parasite that lives in the bile ducts and gall bladder [4]. The clinical signs associated with infection by *Dicrocœlium* are difficult to characterise, as it is most often a case of sub-clinical infection and a combination of different parasite species [4,5]. As adults *D. dendriticum* are located in the bile ducts and gall bladder, the impact often involves hepatic disturbances with increases in liver enzymes, in particular alanine aminotransferase (ALT) and aspartate aminotransferase (AST), regularly demonstrated during natural or experimental infections [6,7]. However, there does not appear to be any drop in haematocrit or plasma albumin when infection levels at necropsy are below 4,000 flukes [8]. In some cases, treatment leads to clinical improvement with a reduction in anaemia and jaundice and an improvement in milk production or body condition score, but these are natural infections associated with multiple parasites so it is difficult to impute the

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clinical signs to *Dicrocœlium dendriticum* alone [7,9]. However, a significant difference in weight was observed in experimentally infected lambs compared with healthy animals [6].

It appears to be a positive association between the number of adult worms in the liver and egg excretion in the animals' faeces [10,11]. Pieragi has also demonstrated a positive association between the number of adult worms and hepatic lesions such as hepatic fibrosis and bile duct hyperplasia [11].

Dicrocœlium dendriticum is a parasite with a complex cycle involving two intermediate hosts, a snail and an ant. Several species of terrestrial gastropods and ants can serve as intermediate hosts for the *Dicrocœlium* cycle [12]. The prevalence of small fluke infection in sheep is linked to the presence of these intermediate hosts.

The prepatent period is 49 to 79 days under experimental infection conditions [10]. Excretion is regular throughout the year, with a slight peak in autumn and winter [3]. Excretion appears to be positively correlated with the number of adult worms present in the animal [10].

In general, the diagnosis is made either by a post-mortem examination focusing on the gall bladder and bile ducts. This enables the adult parasites to be identified directly. Diagnosis can also be made while the animal is still alive by analysing faecal excretion of dicrocoelium eggs. Analysis by flotation requires dense flotation liquid (>1.33) [5,13,14].

Several treatments have been tested to combat dicrocœliosis. Albendazole is the molecule most frequently tested for the treatment of *D. dendriticum* [9,15–17]. This molecule shows efficacy ranging from 92 to 96% reduction in faecal excretion when administered orally at a single dose of 15 mg/kg and 10 mg/kg [16,17], as well as when administered repeatedly at 7-day intervals (99% reduction, [16] or when administered as a sustained-release bolus (88.5% to 91.8% reduction in excretion, [9,15]). However, albendazole at a dose of 5mg/kg appears insufficient to control dicrocoeliosis [18].

Thiophanate and netobimin, two compounds that are metabolised to benzimidazole by animals, have also been shown to be effective against small flukes. Netobimin at a dose of 15 mg/kg or 20 mg/kg showed efficacy of 91.9% and 91.5% respectively [19].This study was carried out to compare the efficacy of two suspensions (5% and 15%) of netobimin against *Dicrocoelium dendriticum* in naturally infected sheep. The efficacy was checked by post-mortem examination twenty-one days post-treatment. The results showed that the efficacy of 5% and 15% suspension of netobimin was 90.80% and 91.50%, respectively, and the use of 15% suspension in sheep is discussed [19,20]) . Thiophanate showed 74.4% efficacy at a dose of 50mg/kg [18].

Praziquantel has also been tested on infected sheep and llamas at a dose of 50mg/kg and appears to be effective [21,22] .

The fact that lead to our study was a faecal egg count carried out after albendazole treatment at a dose of 15 mg/kg. Following this treatment, a coproscopic analysis was carried out on a composite sample to check the parasitic status of the animals. Small fluke eggs were found, leading us to suspect a lack of efficacy of albendazole on this farm. To verify this hypothesis, we therefore decided to test the efficacy of albendazole on this farm more specifically.

2. Materials and Methods

Farm presentation

The study took place on Le Mourier research and innovation site which is a sheep farm in the Limousin region in the centre of France. In this geographical area, the climate is oceanic. The farm, located at an altitude of 300 m, has 50% permanent grassland and 50% temporary grassland. This sheep farm has 700 ewes, half of which are of the Vendéenne breed and the other half F1 (Île de France crossed with Romanov).

This farm is used to treat against *Dicrocoelium* and a faecal examination after a usual treatment leads to a suspicion of lack of efficacy of albendazole against dicrocoelium at 15mg/kg.

Study design, efficacy calculation

Sampling and analysis were carried out in accordance with the recommendations of the World Association for the Advancement of Veterinary Parasitology WAAVP [23]. 15 ewes of the Vendéenne breed, in very good body condition (body condition score above 4) and not pregnant, were included

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in the trial. The animals included in the study were drawn at random, representing each age group. A faecal sample was taken directly from the rectum of these ewes on February 13th 2024 for coprological analysis. The same day, the ewes were weighted individually and orally treated with 15 mg/kg albendazole Valbazen® (Valbazen moutons et chèvres 1,9 %, Zoetis, France) in accordance to AMM recommendations. For each ewe the dosage was adapted to the body weight of the ewe, and the treatment administered with a syringe in order to have a very precise dosage.

The ewes had been grazing for over three months prior to this treatment and remained on pasture for the duration of the experiment. Faecal samples were taken again on February 27th 2024.

Faecal examination:

Samples were stored at room temperature and analysed within 24 hours of collection.

They were analysed using the Mac Master technique modified by Raynaud [24]. 1 gram of faecal material was diluted in 14 mL of flotation liquid with a specific density of 1.45 (LST FASTFLOAT – Pangea UK), with a sensitivity of 15 eggs per gram.

Individual data on faecal egg counts before and after treatment were analysed in the web application (https://www.fecrt.com). Upper and lower 90% confidence intervals (CIs) for the percentage reduction in faecal egg count two weeks post-treatment were calculated using the hybrid Bayesian-frequentist inference method (pairwise study design; research protocol; [25]).

Stool collection and anthelmintic treatments are part of routine veterinary procedures without any traumatic methods, so no specific ethical authorisation was required.

3. Results

All fifteen animals excreted *Dicrocoelium* eggs in the faeces at D0 and D14 after treatment. The excretion values at D0 and D14 are shown in Figure 1. The mean excretion at D0 was 347 eggs per gram with a minimum of 100 epg and a maximum of 1000 epg. At D14, the mean excretion was 211 epg with a minimum of 30 epg and a maximum of 550 epg.

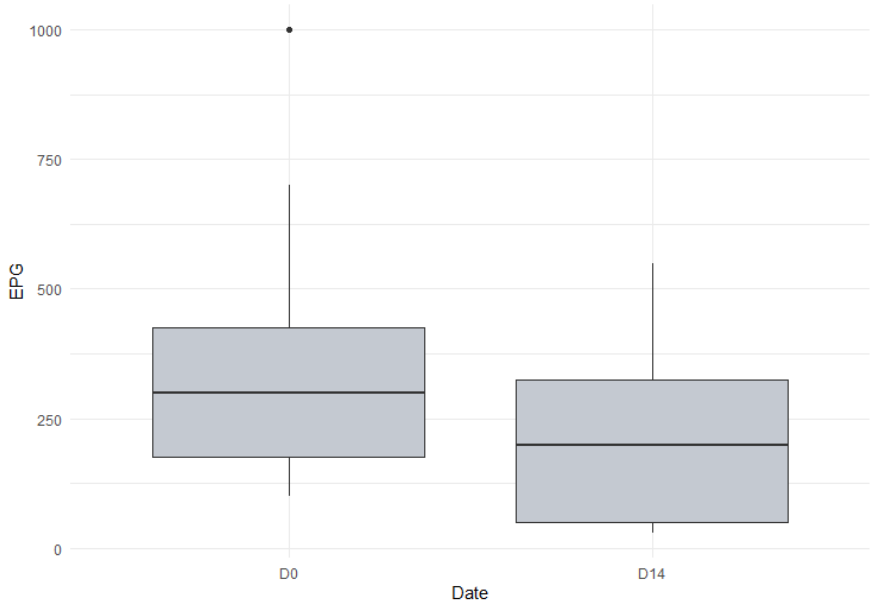

Figure 1. excretion results (epg) at D0 and D14.

The reduction in faecal egg excretion between D0 and D14 was 39% with a 90% confidence interval calculated according to the methods recommended by the WAAVP [13] ranging from -1.1% to 63.2%.

The result of the efficacy test therefore shows that albendazole lacks of efficacy against *D. dendriticum* under our experimental conditions.

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4. Discussion

To date, there has never been a description of lack efficacy of albendazole against small flukes [26] and a recent study still confirms the efficacy of albendazole at 15 mg/kg in a single oral administration against *Dicrocœlium* [17]. This is the first time that an efficacy of much less than 90% has been observed. Previously published studies have reported efficacy above 90 % with this molecule and dosage [16,17].

Albendazole is not effective on larvae [27]. The lack of efficacy observed in our study could be linked in part to the evolution of larval stages into adult stages. However, in studies showing albendazole to be more than 90% effective, the same phenomenon can be observed, especially with Gortva dairy sheep in the Konigova study in which ewes grazed until the beginning of the experiment [17]. It would therefore seem that this phenomenon could explain an efficacy below 100%, but not as collapsed as in our present study.

This initial finding of reduced efficacy of albendazole raises an important issue in sheep farming. The mechanism of action of albendazole is to act on microtubules' polymerization [28]. In other parasite species where the mechanism of action is similar, resistance to one molecule in the family leads to resistance to the whole benzimidazole family [29]. A similar reaction is to be feared for *Dicrocoelium dendriticum*. This would mean that the lack of efficacy is likely to be present for the 3 molecules that have shown activity against the small fluke: albendazole, thiophanate and netobimin. At present, thiophanate and netobimin are no more available in France. This raises the question of the possibility of an alternative treatment for dicrocoeliosis.

It might be interesting to test praziquantel for the treatment of small flukes, this being the only molecule outside the benzimidazole and pro-benzimidazole family [21,22]. The problem is that the dose that seems to be effective corresponds to almost 14 times those used to treat *Moniezia expansa* infections according to manufacturer's recommendations [21,22].

These results also show the importance of verifying the efficacy of treatments by post-treatment faecal egg counts. Since the signs of dicrocœliosis are subclinical and not pathognomonic, it is very difficult to determine whether treatment has been ineffective. This is even more true given that parasitic infections are generally multiple, and the imputability of *Dicrocœlium* is tricky [5,18]. What's more, testing for *Dicrocœlium* requires a dense flotation fluid and is therefore not routinely performed [14].

Dicrocœliosis is a little-studied disease in France. One study on goats carried out in a limited region showed a prevalence of 20% [30]. This prevalence is higher in other parts of Europe. Alkaline soils are favourable to *Dicrocœlium* infestation because they are conducive to intermediate hosts. Although we have a good knowledge of the parasite cycle [12], we have little information on the epidemiology of the disease in France. It would be interesting to improve this knowledge in order to make better recommendations to farmers.

The result of our study showing a reduction in the efficacy of albendazole is problematic because there is no alternative means of management. In fact, it is unthinkable to control intermediate hosts for reasons of ecological impact and cost. The only recommendations that can be made are to avoid total grazing in the morning and evening to limit contact with ants, but this is unthinkable in systems where grazing is continuous over an entire period and the ewes do not return to the barn at night [5].

With the increase of resistance among strongyle species [31,32], mixte grazing is becoming a common recommendation in order to control strongyle population. However, *Dicrocœlium* should be bear in mind while doing grazing with multiple species especially when it involves herds of different origins. All context of mixing grazing herds may be at risk of spreading resistance.

Finally, this first identification of lack of efficacy of albendazole highlights the fact that post treatment faecal egg count in order to check the efficacy of the treatment is necessary. This is important that sheep breeder with lack of efficacy of treatment against *D. dendriticum* stop spend time or money using treatment that are not sufficiently efficient. This highlights also the need of alternative treatment for such parasitic infection.

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5. Conclusions

This is the first report of lack of efficacy of albenzole against sheep infection with *Dicrocoelium dendriticum* in a sheep farm in France. Although albendazole is not effective against the larval stages of small flukes, the reported efficacy of albendazole at 15 mg/kg is generally higher than 90%. The lack of efficacy of abendazole highlights the importance of preserving the efficacy of these molecules by using them only when necessary, and thus improving the diagnosis of dicrocoeliosis. It is also becoming important to regularly check the effectiveness of treatments by post-treatment faecal analysis. As well as improving diagnosis, it is becoming necessary to find alternative methods of controlling *Dicrocoelium dendriticum*. This requires a thorough understanding of the parasite, the epidemiology of infections and the clinical impact, in order to identify new management measures.

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Conflicts of Inerest: The authors declare no conflicts of interest.

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