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Decline in faecal worm egg counts in lambs suckling ewes treated with lipophilic anthelmintics: Implications for hastening development of anthelmintic resistance

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ABSTRACT

The aim for this experiment was to look for evidence of milk transfer of anthelmintic actives from ewes to their suckling lambs by reference to lambs' faecal worm egg count (WEC). The hypothesis was that WEC will decline in lambs suckling ewes treated with anthelmintics known to be lipophilic. One group of lactating Border Leicester × Merino ewes were treated (TX) with a combination of short (2.5 mg/kg monepantel) and long-acting (1 mg/kg moxidectin long-acting injection and a sustained release of 4.62 g albendazole over 100 days) anthelmintics to remove gastrointestinal nematode (GIN) burden on day 0. The other group of lactating ewes (UTX) and all lambs (White Suffolk sires) were not treated. Ewes and lambs grazed as a single group and were exposed to GIN (predominately *Haemonchus contortus*) infection from pasture. Measurements were taken on days 0 and 7. WEC of lambs suckling UTX ewes increased from 6441 to 10,341 eggs per gram (epg) between days 0 and 7, while there was a 51% reduction in WEC for lambs suckling TX ewes. Packed cell volume (PCV) was significantly higher for lambs suckling TX ewes on day 7 compared to lambs suckling UTX ewes (28.5% vs. 24.9%, $p = 0.039$). These results suggest that lambs suckling ewes treated with lipophilic anthelmintics received a sub-therapeutic dose via milk which would increase selection within the GIN (*H. contortus*) population for anthelmintic resistance.

1. Introduction

The prophylactic administration of anthelmintics to ewes, prior to parturition, for treatment and control of gastrointestinal nematode (GIN) infections is a common practice in some regions of Australia. For those treatments containing actives that are lipophilic, excretion in milk represents a potential pharmacokinetic loss. The potential consequences of this loss are a more rapid decline in the concentration of the active in the ewe and the transfer of a portion of the active to the suckling lamb via milk. These issues are discussed in relation to the macrocyclic lactone and monepantel active groups.

The most potent macrocyclic lactone (ML) for treatment and control of GINs is the milbemycin compound, moxidectin. MLs are known to be extremely lipophilic (Alvinerie et al., 1996), allowing for improved drug distribution and an extended half-life (Sutherland and Scott, 2010). When moxidectin is administered to lactating animals, a proportion of the active and its metabolites are partitioned towards the mammary gland and subsequently eliminated in milk (Carceles et al., 2001; Imperiale et al.,

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2004). The area under the concentration–time curve has been reported as being 5 and 10 times greater in milk than in plasma for water buffalo and dairy sheep respectively (Imperiale et al., 2004; Dupuy et al., 2008). The dose fraction of moxidectin recovered from milk in sheep and cattle being 6.5% and 5% respectively (Alvinerie et al., 1996; Imperiale et al., 2004). The greater proportional elimination of moxidectin in milk from sheep compared to cattle may be a result of a higher milk fat content (between 7 and 8%) (Imperiale et al., 2004).

The main metabolite of the parent compound monepantel is monepantel sulfone, which is known to be lipophilic with 6.5–14.4% of the dose administered to lactating ewes excreted in milk and peak concentrations recorded in milk within the first 24 h after administration (European Medicines Agency, 2013).

The presence of these actives in milk suggests that suckling offspring would be exposed to the active without control over the effective dose rate. This raises the possibility of sub-therapeutic doses being ingested by suckling lambs via ewe milk. Sub-therapeutic dosage, as defined by a dose that does not kill the existing GIN burden (Coles et al., 2006), is one of a number of known risk factors for development of anthelmintic resistance (Prichard et al., 1980; Silvestre et al., 2001; Wolstenholme et al., 2004). Another risk factor is the persistency of anthelmintic activity and the duration of depleting concentrations of the active (Abbott et al., 1995; Dobson et al., 1996). This has relevance for suckling lambs which may be ingesting depleting levels of the anthelmintic actives over a prolonged period.

The aim in this experiment was to look for evidence of milk transfer of anthelmintic actives from ewes to their suckling lambs by reference to lambs' worm egg count. The hypothesis being tested was that faecal worm egg counts will decline in lambs suckling ewes treated with lipophilic anthelmintics.

2. Materials and methods

2.1. Experimental design

The experiment is a single factor design using twin-bearing, lactating ewes (treated for GIN infection or untreated) and a random selection of their suckling lambs. Lambing occurred in September, 2013 with lambs identified to the two ewe groups at a mean age of 6 weeks using the Marked Udder Method (Butler, 2004). Ewes and lambs were exposed to GIN infection from grazing and grazed as one group on pasture comprised of perennial ryegrass (*Lolium perenne*), demeter fescue (*Festuca arundinacea*), cocksfoot (*Dactylis glomerata*) and white clover (*Trifolium repens*).

This experiment was conducted between the 13th (day 0) and 21st January, 2014 on a commercial sheep farm on the Northern Tablelands of NSW (30°28′38.90″S and 152°6′45.48″E). This experiment was conducted following approval by the University of New England Animal Ethics Committee (Authority No: AEC12-032).

2.2. Animals

There were 78 lactating, twin-bearing Border Leicester × Merino ewes (mean ± s.e. live weight = 61.5 ± 0.7 kg) with 41 ewes treated with a combination of short and long-acting anthelmintics (TX) and 37 ewes not treated (UTX). Lambs were sired by White Suffolk rams and those included in the experiment were 23 lambs suckling TX ewes and 20 lambs suckling UTX ewes. Remaining lambs ($n = 97$) were not included but remained with the group. Lambs were aged between 3 and 4 months (mean ± s.e. live weight = 31.2 ± 0.6 kg).

2.3. Treatments

2.3.1. Group treatments

On day 0, TX ewes were administered monepantel (2.5 mg/kg, Zolvix® – Novartis Animal Health Australia), moxidectin (1 mg/kg, Cydectin LA® – Virbac Animal Health) and albendazole (4.62 g + 24 mg selenium + 188 mg cobalt over 100 days, Centagard® – Ancare Australia Pty Ltd.). UTX ewes and all lambs were not treated.

2.4. Sampling and measurements

2.4.1. Live weight, faecal worm egg count and coproculture

Lambs were weighed on day 0 and faecal samples collected directly from the rectum on days 0 and 7. Faecal samples were also collected from all UTX ewes and five randomly selected TX ewes on day 7. Individual faecal samples were assessed for faecal consistency and scored in accordance to the classification described by Gordon (1967) which was modified to include half scores. Worm egg count (WEC) were adjusted for faecal consistency as a decrease in faecal dry matter can influence WEC by underestimating the actual number of eggs per gram of faeces present (Le Jambre et al., 2007). Individual WEC were determined using a modified McMaster method (Whitlock, 1948), where 1 egg = 60 epg. From within each ewe treatment group, approximately equal quantities of ewe and lamb faeces from each animal were used and mixed for lamb and ewe group coprocultures. Coprocultures were maintained at 24 °C for 7 days after which larvae were recovered (modified Baerman technique (Dunn, 1969)) and 100 larvae identified to species according to the key of van Wyk et al. (2004).

2.4.2. Blood sample collection and analysis

Blood samples were collected from all lambs and 10 UTX ewes on day 7, via jugular venipuncture into 4 mL EDTA vacutainers (BD Vacutainer®, USA) to determine PCV. Blood samples were analysed within 4 h of collection using the microhematocrit method described by Adams (1976).

2.5. Total worm burden

Eight lambs suckling UTX ewes were selected and humanely euthanised on day 8 to determine the relationship between total worm burden and WEC, and total worm burden and PCV. The small intestine and abomasum were