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Evidence for reversion towards anthelmintic susceptibility in *Teladorsagia circumcincta* in response to resistance management programmes

Dave M. Leathwick, Siva Ganesh, Tania S. Waghorn *

AgResearch Grasslands, private Bag 11008, Palmerston North, New Zealand

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ABSTRACT

Maintaining production and economic viability in the face of resistance to multiple anthelmintic actives is a challenge for farmers in many countries. In this situation, most farmers in New Zealand rely on the use of combination products, containing multiple actives with similar spectra of activity, in order to maintain control. However, there are concerns that use of combinations, once resistance has already developed to the individual actives, could rapidly lead to complete failure of all actives. This study followed seven farms, previously diagnosed with resistance to at least two classes of anthelmintic, which were implementing a tailored programme of 'best practice parasite management'. The aim was to ascertain whether the programmes, which included the almost exclusive use of combination anthelmintics, were able to prevent resistance from developing further. Strategies implemented on each farm varied, but had consistent underlying principles i.e. to avoid over-use of anthelmintics; to minimise parasite challenge to susceptible stock; to maintain refugia of susceptibility and to ensure that only effective anthelmintics were used. Annual faecal egg count reduction tests (FECRT) were undertaken in lambs on all farms to monitor anthelmintic efficacy over 5 years. The efficacy of albendazole, ivermectin and levamisole was calculated and the changes in efficacy against *Teladorsagia circumcincta* assessed. Overall, there was a significant improvement in the effectiveness of both levamisole and ivermectin against *T. circumcincta*, and a positive but non-significant trend in efficacy of albendazole, i.e. there was evidence for reversion towards susceptibility. Hence, the almost exclusive use of combination anthelmintics, integrated with other resistance management strategies, did not result in further resistance development despite all farms exhibiting resistance to multiple actives at the outset. What-is-more, the measured increases in anthelmintic efficacy suggests that adoption of best practice management strategies may extend the useful life of anthelmintics even after resistance has been diagnosed.

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1. Introduction

Anthelmintic resistance in nematode parasites of grazing animals is an expanding problem and is of major concern in many countries (Kaplan, 2004; Waghorn et al., 2006; Besier, 2007; Sutherland and Leathwick, 2011). As anthelmintics are generally the cornerstone of most parasite control programmes, the impact of parasites which are resistant to these drugs can be considerable (Besier, 2007; Sutherland et al., 2010; Miller et al., 2012; Stromberg et al., 2012). In order to retain the effectiveness of anthelmintics for as long as possible, it is essential that strategies are developed and implemented which can slow or prevent the development of resistance (Besier, 2007; Nielsen et al., 2014). With respect to nematode parasites of sheep, there has been extensive research over many years aiming to increase our understanding of the factors influencing the development of resistance, and its management once present (Barnes et al., 1995; Leathwick et al., 2009; Leathwick and Besier, 2014). As a result, for sheep at least, there is an array of established approaches for managing resistance (Leathwick and Besier, 2014).

Historically, one of the main strategies promoted to slow the development of resistance was to alternate (rotate) the class of anthelmintic used on an approximately annual basis (Donald et al., 1980; Prichard et al., 1980; Waller et al., 1989; Coles and Roush, 1992). This recommendation was based on the expectation that if there was a fitness cost associated with being resistant then rotating anthelmintics would allow the opportunity for reversion towards susceptibility to occur in the period when alternative drugs were

* Corresponding author. AgResearch Grasslands, private Bag 11008, Palmerston North, New Zealand. Tel.: +64 6 3518086; fax: +64 6 3518134.
E-mail address: tania.waghorn@agresearch.co.nz (T.S. Waghorn).

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used. Also, it was considered that by not exposing individual worms to more than one class of anthelmintic, selection for resistance to multiple actives was less likely to occur (Prichard et al., 1980). The practice of rotating different anthelmintic classes annually was widely adopted in some countries (Kettle et al., 1983; Waller et al., 1989; Lawrence et al., 2007; Sargison et al., 2007) and is still promoted today in some countries and classes of animals (McMahon et al., 2013a). However, in the interim resistance has continued to develop and resistance to multiple anthelmintic classes is now well established on some farms (van Wyk et al., 1997; Waghorn et al., 2006; Le Jambre et al., 2010; Torres-Acosta et al., 2012; McMahon et al., 2013b; Geurden et al., 2014).

An alternative approach to drug use was suggested by early modelling studies (Smith, 1990; Barnes et al., 1995) which showed that simultaneously using multiple actives, with similar spectra of activity, had the potential to dramatically slow the development of resistance. Subsequently, commercial interests developed and marketted such combination anthelmintic products and these are now used extensively in some countries, but are still not available in others (Bartram et al., 2012; Geary et al., 2012). Subsequent modelling and empirical studies have continued to support the use of combinations to slow the development of resistance (Learmount et al., 2012; Leathwick, 2012; Leathwick et al., 2012). However, both modelling and empirical studies indicate that when the frequency of resistance alleles is already high in a population, combinations lose much of their ability to slow the further development of resistance (Leathwick et al., 2012). This has been used as an argument against the use of combinations (Coles and Roush, 1992) and a perception has developed that their use, once resistance to multiple anthelmintic classes has already established, will result in the further and rapid escalation of resistance to all of the different classes. This perception has created a dilemma for those farmers and their advisors who, prior to the release of new anthelmintic actives (monepantel (Kaminsky et al., 2008) and derquantel (Little et al., 2010)) found themselves in a situation where no single active product would work effectively on their farm and the only products which could be used to maintain control were combinations.

Between 2010 and 2013, a four year extension programme was run to implement and evaluate parasite and resistance management programmes on commercial sheep and beef farms throughout New Zealand (Rhodes et al., 2011). One of the principle aims of this programme was to implement strategies which would maintain or improve on-farm productivity whilst preventing any further increase in the resistance status of parasites on the farms. Given that most of the sheep farms enrolled in this programme already had significant resistance to at least two anthelmintic classes, routine use of combination anthelmintics was inevitable. This situation, therefore, presented an opportunity to follow the progress of anthelmintic resistance on a number of farms under integrated resistance management programmes which included, along with other refugia and management practices, the almost exclusive use of combination anthelmintics.

2. Materials and methods

2.1. The best practice parasite management programme

The Best Practice Parasite Management programme (BPPMP) was an industry-funded programme which aimed to develop and implement parasite and resistance management programmes on a diverse range of farms throughout the country and to evaluate their performance over time (Rhodes et al., 2011). Details of the programme will be published elsewhere, but briefly the intent was to design a parasite management programme specifically to fit the requirements of each farm and farmer, in order to maintain or improve production and profitability, whilst ensuring that the efficacy of anthelmintics did not decline from its initial level.

The programme involved an annual visit to the farm by the farm veterinarian, a parasitologist and an agricultural consultant. A whole-of-farm approach was taken such that at each visit a comprehensive review was undertaken of farm practices and events (e.g. purchase and sale of stock, livestock management, fertiliser applications, and crops grown) over the previous 12 month period along with a detailed review of the current animal health programme. Modifications to the plan were then discussed, informed by any monitoring data, and changes agreed upon for implementation in the following year along with a programme to monitor parasite levels (through regular faecal nematode egg counts (FEC) and coprocultures). Over the following 12 months the plan was implemented by the farmer with assistance from the veterinarians.

2.2. Resistance management strategies

The suite of parasite control and resistance management strategies implemented varied depending on the characteristics of each farm, so no two farms applied the same set of strategies in the same way. There were, however, some consistent underlying principles which can be grouped as:

1. use effective anthelmintic products i.e. on the basis of annual efficacy tests, select products which will achieve high efficacy against all worm species (at least 95%). Because all seven farms were known to have resistance to at least two anthelmintic classes, this required the use of combination products and/or new actives.
2. avoid over-use of anthelmintics i.e. maintain a structured preventive programme of treatments to lambs (Vlassoff and Brunsdon, 1981) with all other treatments on the basis of demonstrated need (i.e. signs of illthrift or FEC) (Leathwick and Besier, 2014).
3. do not administer anthelmintic treatments at intervals shorter than 28 days to allow for some limited contamination of pastures with susceptible genotypes after the pre-patent period of new infection.
4. minimise or eliminate the use of anthelmintics with persistent activity (Leathwick and Besier, 2014).
5. administer a single treatment, containing a new anthelmintic class, to lambs in late summer to remove resistant genotype worms which have accumulated over previous treatments (Leathwick and Hosking, 2009).
6. maximise the opportunities for retention of unselected genotypes (i.e. to maintain refugia). The principal method used to achieve this was to minimise the treatment of adult sheep and ensure that treated lambs and untreated ewes grazed over the same pastures as much as possible. Where this was not practical other approaches were used (Leathwick et al., 2008; Leathwick and Besier, 2014).
7. maximise the use of integrated grazing (cattle, deer, sheep) and crops to minimise parasite challenge to susceptible stock, and adjust anthelmintic treatment schedules accordingly.
8. ensure that anthelmintic treatments did not coincide with a shift to pastures likely to have low numbers of infective larvae unless other strategies were in place to ensure adequate refugia (e.g. treated lambs followed by untreated adult sheep) (Waghorn et al., 2009).
9. effective quarantine procedures to prevent the introduction of resistant genotypes with stock transferred onto the farm (Leathwick and Besier, 2014).

Following each annual visit by the advisory team, throughout the course of the programme, each farmer was allocated a subjec-

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