



Multiple-active anthelmintic formulations: Friend or foe in sustainable parasite control?[☆]

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ABSTRACT

Multiple-active anthelmintic formulations (combinations of anthelmintics with a similar spectrum of activity and different mechanisms of action and resistance) are widely available in several regions of the world for the control of sheep nematodes. There are two main justifications for the use of such combinations: (i) to enable the effective control of nematodes in the presence of single or multiple drug resistance and (ii) to slow development of resistance to the component anthelmintic classes. Computer model simulations of sheep nematode populations indicate that the ability of combinations to slow development of resistance is maximised if certain prerequisite criteria are met, the most important of which appear to concern the opportunity for survival of susceptible nematodes in refugia and the pre-existing levels of resistance to each of the anthelmintics in the combination. The question then becomes whether these criteria are likely to be fulfilled under field conditions. Concerns include the potential to select for resistance to multiple anthelmintic classes concurrently if there are insufficient parasites in refugia, the potential for shared mechanisms of resistance between chemical classes of anthelmintics, the need for further empirical validation of computer simulations, the pre-existing frequency of resistance alleles which may be too high on some farms to warrant introduction of certain combinations and the potential encouragement of farmers to prepare their own mixtures and/or neglect other management principles for sustainable parasite control. In conclusion, multiple-active formulations can play an important role in resistance management. However, they are not a panacea and should always be used in accordance with contemporary principles for sustainable anthelmintic use.

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1. Introduction

Anthelmintic resistance in nematodes of small ruminants is a global problem that poses a significant threat to the production and welfare of grazing livestock (Besier, 2007; Papadopoulos et al., 2012; Torres-Acosta et al., 2012). Of particular concern is the escalating level of resistance to the macrocyclic lactones, as well as reports of

multiple resistance, i.e. to more than one anthelmintic drugs. Anthelmintic treatment provides a survival advantage for parasites carrying resistance alleles. Surviving parasites pass these alleles to their offspring, so the allele frequency increases during subsequent parasite generations if selection is maintained. It is generally considered that anthelmintic resistance develops through selection of ancient resistance alleles present in the parasite population. However, spontaneous recent mutations, which may occur, and the introduction of resistance alleles as a consequence of movement of hosts, may also play an important role (Gilleard and Beech, 2007).

In this context, the administration of combinations of anthelmintics with a similar spectrum of activity and

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different mechanisms of action and resistance development has been suggested as a potential means of delaying the development of anthelmintic resistance (Bartram et al., 2012). For the purposes of this paper, the term ‘multiple-actives’ refers to formulations that contain a mixture of two or more distinct classes of anthelmintics with a similar spectrum of activity, rather than combinations formulated to provide broad-spectrum control of parasites from different phyla, e.g. nematodes and tapeworms or nematodes and liver fluke. Multiple-actives are commercially available in Australia, New Zealand, South Africa, Latin America and the United Kingdom and include dual combinations of levamisole and macrocyclic lactone, levamisole and benzimidazole, derquantel and macrocyclic lactone or benzimidazole and levamisole and macrocyclic lactone.

There are two main justifications for the use of multiple-actives: (i) to enable the effective control of nematodes in the presence of single or multiple drug resistance and (ii) to slow development of resistance to the component anthelmintic classes (Leathwick et al., 2009). These effects occur because one component of the formulation eliminates parasites with alleles that confer resistance to one or more of the other components; alleles conferring resistance to all components must arise in the same parasite for it to survive. The survivors are then diluted by unselected parasites in refugia (van Wyk, 2001). The rationale for using drug combinations to delay development of anthelmintic resistance was initially inspired by research into insecticide resistance, which supported the concept that use of insecticides in combination can greatly extend the effective life of the constituent chemicals, provided certain conditions would be met.

In this context, the following six conditions have been identified, under which multiple-active formulations will remain effective (Leathwick et al., 2009): (i) resistance to different chemical classes of pesticide is under independent genetic control, i.e. no cross-resistance, (ii) resistance alleles are functionally recessive under treatment, (iii) there is a low frequency of resistance alleles, (iv) the efficacy of each of the component pesticides against susceptible genotypes approaches 100%, (v) a proportion of the population is not exposed to treatment to ensure that surviving resistant genotypes are diluted in a pool of susceptible genotypes and (vi) the pesticides used have a similar duration of action so that all components are effective throughout the duration of efficacy of the combination (Wood and Mani, 1981; Curtis, 1985; Mani, 1985; Comins, 1986; Roush, 1989). Importantly, these conditions interact so that all are not universally required for a combination to be effective in slowing the development of resistance (Wood and Mani, 1981). The question then becomes whether the conditions required to achieve the potential benefit from multiple-actives are likely to occur in the context of the use of anthelmintics to control nematode parasites of livestock.

2. Resistance to different chemical classes is under independent genetic control

It is generally accepted that mechanisms of resistance to benzimidazoles, levamisole and macrocyclic lactones

are different and there is virtually no cross-resistance between them (Mottier and Prichard, 2008). Evidence is provided by data demonstrating higher efficacy of one anthelmintic class against nematode populations resistant to other classes or by the additive effects of anthelmintics when different classes are administered in combination (Le Jambre et al., 2010). Evidence has also been presented that repeated selection of *Haemonchus contortus* with macrocyclic lactone anthelmintics can cause allelic changes in the β -tubulin isotype 1 gene, the key locus involved in the mechanism of benzimidazole resistance (Mottier and Prichard, 2008), but it is far from clear whether these findings represent true cross-resistance. Moreover, computer simulation indicates that a degree of cross-resistance between two anthelmintic classes does not necessarily negate the benefit of using actives in combination compared with using them separately either sequentially or in rotation (Leathwick, 2012). Indeed, development of resistance was delayed when both drugs were used in combination, even in the presence of a common allele which was selected for by both drugs.

3. Resistance alleles are functionally recessive under treatment

When resistance is functionally dominant under pesticide treatment, it has been suggested that use of combinations would result in the rapid build-up of resistance due to linkage disequilibrium (Curtis, 1985). However, the non-random accumulation of resistance genotypes in Curtis’s model was influenced by the assumption that 90% of each insect generation was exposed to treatment prior to mating and, hence, there was relatively little opportunity for resistant genotypes to be broken up by mating with susceptible genotypes. This conclusion was supported by another modelling study, in which importance of functional dominance in influencing the rate of development of resistance was reduced as the proportion of the population escaping exposure to treatment increased (Wood and Mani, 1981). Resistance to benzimidazoles, levamisole and macrocyclic lactones is generally regarded as being recessive or partially recessive, with the notable exception of ivermectin resistance, which behaves as a dominant trait in some parasites (Sutherland et al., 2002). Modelling of anthelmintic resistance in sheep nematode indicated that combinations profoundly slowed development of resistance, even when resistance was functionally dominant or partially dominant (Smith, 1990; Barnes et al., 1995; Leathwick, 2012). Probably, this was due to the small proportions of the populations exposed to each treatment and the normally rapid re-infection of treated animals with susceptible larvae on pasture.

4. Low frequency of resistance alleles

The frequency of resistance alleles will vary enormously between countries, farms, even between parasite species on a farm (Leathwick et al., 2009). While multiple-actives have the greatest ability to slow development of anthelmintic resistance when resistance genes are rare, computer modelling of sheep nematode

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