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Research in Veterinary Science 78 (2005) 99–108

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Anthelmintic resistance – looking to the future: a UK perspective

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Abstract

The full extent of anthelmintic resistance in nematodes of farm animals is not known. Resistance can be detected with a faecal egg count reduction test and two in vitro tests, the egg hatch and larval development tests. The sensitivity of these two in vitro tests can be increased by using discriminating doses rather than calculating LD_{50} values. Only benzimidazole resistance can be detected with PCR based tests because the molecular mechanisms of resistance to levamisole and the macrocyclic lactones remain unknown. Resistance detection is important because it enables the appropriate management strategies to be put in place. The development of resistance is delayed by keeping sufficient parasites in refugia (not exposed to anthelmintic), but the necessary management details have not yet been validated in the field. It is probably too late to use combination products to delay the development of resistance, except in cattle but quarantining animals to prevent introduction of resistant helminths onto a farm is important. Dilution of resistant worms with susceptible ones is only at the preliminary research stage and the application of non-chemical methods of control to delay resistance is not yet a practical option. Extensive research is required to manage resistance, especially in the control of resistance in *Fasciola hepatica*.

Keywords: Anthelmintic resistance; *Fasciola*; FECRT; Genetics; Nematodes; Refugia; Resistance tests; Surveillance

1. Introduction

Antibiotic resistance has quite correctly become a major political issue because human lives are being placed at risk due to the development of bacteria that are not controlled by existing antibiotics. There has also been a large international commitment to improve the control of malaria which is a major killer of young children, particularly in Africa. As with bacterial infections, the failure of existing antimalarials combined with insecticide resistance is the major issue in malarial control. The almost inevitable failure of vital drugs in humans is raising the realisation in funding agencies on an international level that the development of resistance to chemicals has to be addressed seriously in all cases of human and animal infections and infestations with parasites. As revealed by sales figures in many countries, parasites are the major health issue in most farm animals. Despite this, veterinary parasitology has been in decline for a relatively long period (Coles, 2001) due largely to the availability of excellent drugs, especially the macrocyclic lactones, for killing ecto- and endo-parasites. It is to be hoped that this trend in veterinary parasitology will be reversed in order that trained personnel are available to address the large practical problems that are developing. It is, therefore, timely to ask what can be done to slow or reverse the seemingly relentless rise of anthelmintic resistance in both nematodes and liver fluke.

2. Current information

There have been a number of reviews on anthelmintic resistance that have documented the available information on the species of nematodes to which resistance has been detected, to which drugs it had developed and in what countries it has been found (e.g. Prichard,

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doi:10.1016/j.rvsc.2004.09.001

1994; Condor and Campbell, 1995; Jackson, 1993; Jackson and Coop, 2000; Kaplan, 2002; Sangster, 1999; Waller, 1997). Determining the extent of resistance depends on the existence of tests to detect resistance and standardised tests for resistance were prepared by the World Association for the Advancement of Veterinary Parasitology (WAAVP) in 1992 (Coles et al., 1992). A review of the existing in vitro tests for resistance was published recently by Taylor et al. (2002). Past research has looked at factors which may affect the rate of development of resistance and based on this, recommendations were made to slow the development of resistance (e.g. Coles and Roush, 1992; Coles, 2002a). It now appears that some of the advice given on nematode control, particularly in the southern hemisphere, may have accelerated the development of resistance. For example, the recommendation to treat at the beginning and end of the dry season (Waller et al., 1995) will probably result in the next generation of worms coming only from those exposed to anthelmintic.

3. Factors affecting the development of resistance

There are four features determining how fast resistance develops in the field, (1) the numbers of worms in refugia, (2) the gene frequency for resistance in untreated populations, (3) whether resistance is dominant or recessive and (4) the biological fitness of resistant worms compared with susceptible ones.

3.1. Nematodes in refugia

The major issue in the development of resistance and the one that can be affected by management is the percentage contribution that nematodes, or any other parasite for that matter, that survive treatment make to the next generation. This will be affected by the numbers of worms escaping treatment (considered under Section 6.1). Any action that increases the percentage contribution that survivors of treatment make to the next generation, such as frequent use of anthelmintics, will enhance the development of resistance and conversely actions that ensure the next generation comes from untreated worms will slow the development of resistance.

3.2. Gene frequency in unselected nematodes

Although they may look identical a population of one species of nematodes is in fact genetically diverse (Grant, 1994). Amongst the genetic diversity there may occasionally be mutations in the receptor sites where anthelmintics work or differences in enzymes or mechanisms that may affect the metabolism or transport of the anthelmintics. In a population of nematodes exposed regularly to a drug this will confer an evolutionary advantage to the worms with the altered genome. Just how common the mutation (or mutations) is that confers resistance to a particular drug in a unselected population of worms is not known, but in horses it has been suggested that in the order of 3% of cyathostomins in wild (naïve) worm populations could be resistant (rr genes) and 17% be heterozygotes (rs) (Pape et al., 2003). Because the molecular basis of benzimidazole resistance is not fully understood in cyathostomins, further research is required to confirm this interpretation of the data. The apparently high level of resistance in unselected populations could explain why benzimidazole resistance appears to have emerged relatively rapidly. Regional differences in the susceptibility of parasites to chemotherapy suggest that gene frequency for resistance can differ from area to area before a drug is used. For example, higher doses of oxamniquine are required to kill *Schistosoma mansoni* in East Africa than in Brazil. Reasoning that this must represent more genes were present for resistance in East Africa, Coles et al. (1987) looked for oxamniquine resistance in Kenya and found it in populations where little or no oxamniquine had been used. It actually turned out that resistance in *S. mansoni* is associated with a loss of an enzyme to activate oxamniquine rather than a genetic mutation conferring resistance to the drug (Cioli et al., 1993), but the principle of regional differences in distribution of genes for resistance still applies. The very limited information on natural gene frequency for resistance stems both from the lack of highly sensitive tests to detect resistance to the major anthelmintics, except benzimidazoles, and the very few populations of commercially important nematodes that have not been exposed to anthelmintics.

3.3. Genetics of anthelmintic resistance

Resistance will develop faster if genes for resistance are dominant rather than recessive (numerical examples are given in Coles et al., 2004). Benzimidazole and levamisole resistance in an isolate of *Haemonchus contortus* resistant to both anthelmintics was incompletely recessive (Sangster et al., 1998). The recessive nature of levamisole resistance agrees with the conclusion of Martin and McKenzie (1990) using *Trichostrongylus colubriformis*. Herlich et al. (1981) also concluded that cambendazole resistance in *H. contortus* was recessive. However, Le Jambre et al. (1979) reported that thiabendazole resistance in *H. contortus* was semi-dominant and in *T. colubriformis* it was co-dominant (Martin et al., 1988). The differing results may reflect the selection history of the worms prior to the experiments but also point to more than one gene frequently being involved. Resistance to ivermectin in *H. contortus* was completely dominant (Le Jambre et al., 2000) which is unfortunate given the very high use being made of the macrocyclic lactones in sheep and catle farming.