Anthelmintic resistance: a perspective on our current understanding and ability to control this problem

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Abstract

Regimens to prevent the development of anthelmintic resistance (AR) have been promoted for many years. All reflect some appreciation of the selection pressure that different anthelmintic treatment policies apply to nematodes but AR is clearly more complicated than this for reasons we still do not yet understand sufficiently well. Whilst managing a refugia population on a farm is important to limit the development of AR there are many aspects that are not understood. Why is AR more common in some species than others, especially for some such as *Dictyocaulus* where there is clearly a short-lived refugia population and heavy selection pressure yet no recorded AR. The cost of AR to farmers has slowly escalated over the years and using a New Zealand example it can be estimated for a typical sheep farm that the cost of using a single active of an older anthelmintic such as levamisole compared to a newer anthelmintic such as monepantel is about NZ$3.27 per lamb raised. Diagnosis of AR continues to largely rely on the use of faecal egg count reduction tests. These are a very crude tool but generally acceptable for sheep. However, for cattle and farmed deer it is difficult to get egg counts high enough to conduct a meaningful test. Clearly more effort is needed to understand the mechanisms associated with AR and to develop better diagnostic tests so that farmers with their advisors are better able to achieve sustainable helminth control.

Keywords Anthelmintic resistance; sheep; cattle; deer; cost of anthelmintic resistance; diagnosis of anthelmintic resistance

Introduction

Anthelmintic resistance (AR) is a subject that has been extensively reviewed over many years (Kaplan & Vidyashankar 2012; Leathwick et al. 2001; Leathwick et al. 2009; Leathwick and Besier 2014; Besier 2007). Initial reports indicated it was primarily a problem for small ruminants (sheep and goats) but studies from the 1990s onwards clearly showed that there was also a potential problem with helminths in cattle as well (Sutherland & Leathwick, 2011). However, the problem extends beyond the traditional sheep and cattle industries as in the New Zealand context there is also an issue with reduced anthelmintic efficacy to treat parasites of farmed deer (Mackintosh et al. 2014). Indeed, deer farmers in New Zealand are currently struggling to find anthelmintics that are fully effective and are arguably in a more difficult situation than either sheep or cattle farmers. In addition, there are well-established issues with AR in horse parasites (von Samson-Himmelstjerna 2012; Scott et al. 2015) and pig parasites (Bauer & Gerwert 2002; Gerwert et al. 2002) and especially for the former these are progressively getting more severe.

Simplistic explanations as to why nematodes develop resistance, and recommendations to limit the development of AR, have been promoted for many years. All reflect some appreciation of the selection pressure that different anthelmintic-treatment regimens apply to nematodes but it is clearly more complicated than this for reasons we do not yet fully understand. We also apply these same recommendations for preserving the efficacy of all anthelmintics, regardless that they have different modes of action and consequently different genetic changes associated with AR. This holistic approach is likely to mask important differences between anthelmintic groups. A common recommendation in recent years is to maintain a refugia population of unselected nematodes in the animal's environment so that any survivors of a treatment are less likely to mate with other survivors but rather mate with newly-ingested, unselected, hopefully non-resistant, nematodes (Sutherland 2015). Any progeny would then be heterozygotes and our current belief for most anthelmintics is that resistance is largely recessive and consequently these heterozygotes would be successfully killed with a standard dose of anthelmintic. In one recent study, aggressive manipulation of farm management to ensure an effective refugia population is present has recently been shown to reverse the trend towards more severe AR developing on New Zealand sheep farms (Leathwick et al. 2015) which clearly supports this general approach. However, most reports of AR to benzimidazoles and levamisole show it is remarkably stable and doesn't revert to susceptibility very quickly (Leathwick et al. 2001).

Variation among species

If development of AR was only about a lack of a refugia, then nematodes such as those in the genus *Dictyocaulus,* which includes several species of lungworms in ruminants, could be expected to have commonly developed resistance. The free-living stages are relatively short-lived compared with other trichostrongylid nematodes, indicating that any refugia will die off quickly. This genus is particularly susceptible to macrocyclic lactone (ML) anthelmintics resulting in long persistent activity of topically applied products. In New Zealand, where young calves are often treated at 4 weekly intervals (Bisset 1994, Jackson et al 2006), this would effectively amount to suppressive treatment in the absence of a refugia population if the anthelmintic used was a topically applied ML which has commonly been the practice. Both of these factors are generally considered highly selective for AR yet there are no formal reports of AR in this genus anywhere. In the genus *Trichostrongylus* in New Zealand sheep, we see AR in *Trichostrongylus colubriformis* much more frequently than in *Trichostrongylus vitrinus* despite recent research showing both species are commonly found on farms throughout the country and this difference in AR appears to be for all types of anthelmintic (Waghorn et al. 2014). There is no current hypothesis to explain this difference.

For sheep and goats, different nematode species have emerged as being anthelmintic resistant in different geographical areas and the rationale for this also isn't entirely clear as yet. In New Zealand resistance to any anthelmintic in *Haemonchus contortus* is surprisingly rare (McKenna 2016) yet it is the most commonly resistant species in warmer areas such as central/northern Australia and the tropics (Playford et al. 2014). In New Zealand we do see *Haemonchus* in sheep and goats over the summer months and regularly see clinical disease on a few farms at least. It might be thought the poor survival of free-living stages over winter in New Zealand would lead to higher levels of resistance due to a lack of refugia with a consequent genetic bottleneck but that hasn't been the case. Clearly we have barely scratched the surface in our understanding of the issues around AR.

Cost of anthelmintic resistance on farm

As for all issues around AR there has been much debate about the actual cost to the farmer. Within New Zealand it is possible for sheep farmers to at least estimate the cost of purchasing anthelmintics using mean figures for farm size, lambs born and sold etc. The following estimates relate to a North Island property with 7500 adult ewes, keeping 1500 young female sheep (hoggets) as replacements. The lambing percentage of the ewes is 130% and for the hoggets is 85%. This provides a total of about 11000 lambs for sale each year. Typically, lambs are sold progressively from weaning onwards until just the replacement stock are on the farm by one year of age. We also know that young lambs in New Zealand receive 5-6 anthelmintic treatments at 28-day intervals from weaning, and then usually a further 1-2 treatments from 12 to 18 months of age (Lawrence et al. 2006). After this time, adult sheep don't commonly require treatment. Estimating the cost of anthelmintic treatment for these young sheep on this typical farm arrives at a cost of drug of NZ$2,230 if using a single action older anthelmintic such as levamisole (NZ$0.0014/kg live weight), NZ$10,412 if each treatment is using one of the commercially available triple combinations of abamectin+benzimidazole+levamisole (NZ$0.007/kg live weight) and NZ$38,376 if each treatment is with "Zolvix Plus" (monepantel+abamectin; Elanco Animal Health, New Zealand; NZ$0.0258/kg live weight). For international readers the exchange rate is about NZ$1=US$0.70. New Zealand has had access to commercially formulated combinations of anthelmintics for many years and industry sources indicate that triple combinations of the original three action families, as indicated above, are now the preferred choice for many farmers, generally because other single or dual action products are no longer fully effective. Consequently, most farmers are currently paying a price for the presence or threat of AR. The development of the new anthelmintic monepantel now allows a direct comparison of at least the cost of treatment for when the older anthelmintic types are no longer effective. The other more recent anthelmintic type represented by "Startect" (derquantel+abamectin; Zoetis New Zealand Ltd) is a similar price to "Zolvix Plus". To put this into some other perspective the difference between being able to use straight levamisole and needing to use "Zolvix Plus" for this typical farm is ~NZ$36,000 which is a large proportion of the salary of one labour unit on a farm. In another sense, that equates to approximately NZ$3.27 per lamb raised on this farm which if extrapolated to the whole country where about 20×10^6 lambs are raised each year would be a large expense.

The only recent data we have on the prevalence of AR in New Zealand is from laboratory data based on results of faecal egg count reduction tests (FECRTs; McKenna 2016) and hence is invariably biased. Nevertheless, accepting this it indicates that about 6% of farms tested now have *Teladorsagia* which are resistant to the triple combination of abamectin+benzimidazole+levamisole suggesting they have reached the point indicated above where they need to consider the more expensive anthelmintic option. By comparison FECRT results indicate 45% of farms have no recorded resistance in any parasite to levamisole but this is probably an underestimate based on an earlier survey in 2004/5 (Waghorn et al. 2006). Sales of commercial product containing just a single active ingredient have declined dramatically in recent years in New Zealand in line with the perception that AR has progressed to the point where at least combinations of anthelmintics are required.

For New Zealand sheep farmers, there is the added cost of undiagnosed AR where a farmer continues to use an anthelmintic which is no longer fully effective. It is difficult to put a realistic industry cost on this but it will invariably be higher than the cost of using a fully effective treatment in the author's opinion. Two studies comparing lambs being treated with a partly effective treatment versus an effective treatment showed a 10-14% reduction in carcase value when lambs were killed (Sutherland et al. 2010; Miller et al. 2012). So either a reduced value is apparent or lambs will take longer to reach the same slaughter weight. Either way there is a cost to the farmer from using an ineffective anthelmintic.

Diagnostic limitations for anthelmintic resistance

Diagnosis of AR continues to largely rely on the use of FECRTs (Coles et al. 2006). These are a very crude tool but generally acceptable for sheep. However, for cattle it is difficult to get egg counts high enough to conduct a meaningful test and the same situation applies to farmed deer. Consequently, whilst there have been a reasonable number of FECRTs conducted with sheep in New Zealand (21% of farms; Corner-Thomas et al. 2015) there have been very few with cattle despite recent studies demonstrating the existence of ML-resistant *Ostertagia ostertagi* in New Zealand (Waghorn et al. 2016). This demonstration of ML-resistant *O. ostertagi* poses a significant risk for both dairy and beef cattle within New Zealand but the absolute majority of cattle farmers remain ignorant of the status of cattle nematodes on their farm. The recent development of a multiplex PCR to diagnose gastrointestinal nematode infection in cattle (Roeber et al. 2017) may assist with diagnosis in cattle. However, there are currently no simple molecular tests to recognise resistant nematodes, except perhaps with benzimidazoles, so it will still be necessary to use some phenotypic assay to demonstrate AR then possibly the use of molecular tools to assist with more accurate identification of nematodes. There is clearly a need to further refine the diagnosis of AR in all hosts.

Conclusion

Collectively it might be thought these issues and potential costs would see AR, and the drive to achieve more sustainable parasite control, as key research topics in a country with a large ruminant industry such as New Zealand. In a recent survey, sheep farmers in New Zealand rated "internal parasites" as their second highest-ranked suggested research topic (forage type/system was the highest; Greer et al. 2015). However, research effort in New Zealand does not reflect this perceived importance. The situation around the world largely reflects the New Zealand experience.

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