Review of deer anthelmintics

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Abstract

Lungworm [Dictyocaulus] infections are potentially a major problem under New Zealand deer farming conditions Gastrointestinal nematode infections can significantly affect deer production also. Preventive drenching strategies using effective anthelmintics are used to control these problems. Three benzimidazoles (BZ) and four macrocyclic lactone (ML) (avermectin-milbemycin) anthelmintics are currently marketed in New Zealand with a label claim for use in deer There is, however, remarkably little published trial data on the efficacy of anthelmintics against deer parasites Most of the studies that are directly applicable to New Zealand deer farming systems and the associated parasite problems have been carried out here Nevertheless, the published information on efficacy of the anthelmintics currently used ranges from barely adequate to non-existent. The information available is reviewed and the implications of what is known and unknown are discussed.

Introduction and background

When deer farming first became a commercial reality around 25-30 years ago, there was speculation about what might emerge as animal health problems Among these, of course, was parasitism, particularly nematode parasitism I recall thinking at the time that gastrointestinal parasites would be most likely to prove a problem with deer being fenced in and relatively densely stocked. However, it very quickly became clear that it was lungworm, Dictyocaulus, spp infections that were by far the most serious problem and that gastrointestinal parasitism was considerably less so Outbreaks of parasitic bronchitis occurred frequently, particularly in young deer in the autumn and deaths were common Subsequently it was shown that although GI parasites seldom cause clinical disease or deaths, they can have a significant effect on growth of young deer They also appear to be involved in some way in what was referred to as the 'fading elk' syndrome although their precise role remains unclear

Deer harbour a range of abomasal nematode parasites belonging to the genus Ostertagia or, more commonly, related genera such as Spiculopteragia and Skrjabinagia. To simplify things these are generally referred to as Ostertagia-type nematodes Small intestine nematodes, notably species of Cooperia, also occur but these are less numerous and less important than the abomasal parasites

The other thing that emerged very early in the piece was that treating deer for lungworm was not that straightforward and some drugs, such as levamisole, that were effective in cattle were not so in deer. There were even suggestions, largely based on anecdotal reports, that the second and third generation benzimidazoles that became available in the mid-1970's were not always effective (Wilson & Collier, 1981) There were also reports from overseas involving other deer species indicating that anthelmintic doses higher than those used in cattle were required (e g Presidente et al 1973)

It was suggested that reduced efficacy might be because deer metabolise drugs more rapidly than cattle (Charleston, 1980) Experimental evidence for this in relation to levamisole was subsequently reported (Mason, unpublished, cited by Mackintosh et al 1984), and it was also shown that deer metabolise and excrete oxfendazole much more rapidly than do sheep (Watson & Manley, 1985). Similar results were obtained with albendazole (Waldrup et al 1997) However, I am not aware of any direct comparisons with cattle regarding the BZ's although the observation that at least some deer species need higher doses than cattle to give comparable efficacy does suggest that deer may be more efficient at detoxification of BZ's than cattle

By the mid-1980's there was a range of potent, broad spectrum BZ's, including mebendazole, fenbendazole, oxfendazole, febantel and albendazole available, and the first of the macrocyclic lactones (ML) (the avermectin-milbemycin action-family), ivermectin By that time too, recommendations for preventive drenching in the post-weaning period were being adopted and

proving effective in reducing the seriousness of parasitism in young deer Since then, other ML's have been developed and included in the armoury, and some trial work has been done with intrarumenal bolus, slow-release products containing BZ's.

In practice, the way these drugs are used on deer farms is extremely variable both in terms of the pattern and frequency of anthelmintic treatments. This has been analysed and reviewed in detail elsewhere (Wilson et al 1997; Audigé et al 1998) and will not be covered here.

Which brings us up to the present day and my task of reviewing the anthelmintics that are currently available for use in deer As noted earlier, it is not my brief to cover treatment recommendations or regimes but rather the relative merits of the various drugs that can be used This proved by no means as easy as it sounds as it soon became clear that the amount of published information on the efficacy of anthelmintics in deer is astonishingly small A search of the literature using CAB abstracts from 1973 to 2001 revealed only about 200-250 published papers dealing with anthelmintics of any kind in any type of deer, whether farmed, managed range or wild, anywhere in the world[1] To put this in perspective, there were over 26000 citations dealing with anthelmintics and over 10,000 dealing with deer[1]

So there isn't a lot to go on For some anthelmintics with registered claims in New Zealand there appear to be no published data on efficacy This does not mean that there are none, as presumably some have to be provided for registration of a claim, but that they have never made it into the scientific literature For other anthelmintics, much of the published information does not relate to the species of deer or the parasites that we are concerned with or farming conditions comparable with ours All this makes any critical evaluation of claims made for anthelmintics in deer difficult to say the least and this needs to be borne in mind in what follows

The anthelmintics currently on the market with a label claim for use in deer in New Zealand are listed in Table 1 and fall into two categories, benzimidazoles (BZ's) and macrocyclic lactones (ML's). I propose to look at these in turn and see what we can make of the information that is available. For the sake of clarity I shall deal with efficacy against lungworm and gastrointestinal parasites separately.

Table 1: Anthelmintic formulations currently available with a label claim for use against nematode parasites of deer[as listed in the Index of Veterinary Specialities 2001]

Drug	Product Name ®	Company	Dose Rate
Albendazole	Albendazole C	Ancare	10 mg/kg
	Valbazen	Schering-Plough	10 mg/kg
Fenbendazole	Axilur	Intervet	7 5 mg/kg
	Panacur [including mineralised forms	Intervet	7 5 mg/kg
Oxfendazole	Bomatak-C [incl Mineralised forms]	Bomac	4 5 mg/kg
	Oxfen [incl mineralised forms]	Ancare	4.5 mg/kg
	Spectre [± Se]	Schering-Plough	4.5 mg/kg
	Systamex Low Dose [± Se, minerals]	Schering-Plough	4 5 mg/kg
Ivermectin	Ivomec Pour-on for cattle and deer	Merial	0 5 mg/kg
Eprinomectin	Ivomec Eprinex Pour-on for cattle and deer	Merial	0 5 mg/kg
Moxidectin	Cydectin Pour-on	Fort Dodge	0 5 mg/kg
	Vetdectin Pour-on	Fort Dodge	0 5 mg/kg
Abamectin	Genesis Pour-on for cattle and deer	Ancare	0 5 mg/kg

The Benzimidazoles

The BZ's currently available in New Zealand and with a label claim for the treatment of deer are albendazole, fenbendazole and oxfendazole All are what are known as third generation benzimidazoles and have a broad spectrum of activity against nematodes in ruminants. Although their use in sheep has fallen markedly in recent years as a result of anthelmintic resistance concerns, a survey of lower North Island deer farms in 1992-4 indicated that they were still commonly being used for deer (Audigé et al 1998) and I imagine they still are All are formulated as oral drenches.

Febantel, a pro-benzimidazole that is metabolised to fenbendazole and then oxfendazole for its activity, has been used in deer (Mackintosh & Mason, 1985) but is no longer marketed for ruminants in New Zealand Slow-release boluses containing albendazole (Proftril ® SmithKline Beecham NZ Ltd) which were trialled in weaner deer in the early 90's (Rhodes 1993; Waldrup et al 1993, 1994), and one containing morantel tartrate tested in wapiti (Waldrup & Mackintosh 1993) are also no longer available Concentrate feed medicated with albendazole has also been tried (Anderson & Wilson 1984)

Albendazole

A survey of anthelmintic use in 1981 showed that albendazole was being used on approximately 22% of 130 farms surveyed (Mason & Gladden, 1983) and on four (25%) of the 16 farms studied by Audigé et al (1998). Most of the trial work on its efficacy has been carried out in New Zealand and reported in the proceedings of earlier Deer Branch Conferences, but most of it based on faecal egg and larval counts and not always presented in detail The situation is further complicated by the indications that the drug behaves differently in different types of deer (Waldrup et al. 1997)

In general, the trial work suggests that at the recommended dose-rate (10 mg/kg), albendazole will substantially reduce the shedding of lungworm larvae in red deer to very low levels, It does not always eliminate itshedding completely in all animals (Anderson & Wilson, 1984; Mackintosh et al. 1984, Mason & Beatson, 1985) However, the only slaughter trial data available showed rather poor efficacy – less than 85% on an arithmetic mean basis [and even less calculated from geometric means] - against adult and immature lungworms in red deer and F1 red/wapiti hybrids. In the latter, efficacy against larval lungworm was very low. In wapiti the efficacy against both adult and larval lungworm was zero (Waldrup et al. 1997). In addition some wapiti died from acute lungworm infection 7-16 days after treatment

At first sight this relatively poor efficacy in red deer may seem difficult to reconcile with the observations on larval excretion rates But since BZ's are known to affect the development and hatching of strongyle eggs, presumably they could reduce the hatching of first stage lungworm larvae in the lung and their viability in their passage along the gut If so, this could reduce the numbers of larvae excreted and/or our ability to detect them in faeces (which depends on them being alive and active) so that the decrease in larval numbers is greater than would be accounted for by the removal of adult worms If this were a real effect, it would, of course, apply to all BZ's.

From the egg count data available, it would appear that albendazole is generally more effective against gastrointestinal nematodes in red deer (Anderson & Wilson, 1984) although again there is precious little to go on The results of slaughter trials have been somewhat variable. In one there was a 95% reduction in adult abomasal Ostertagia-like worms (based on geometric means) but only 75% efficacy against L4's (Waldrup et al 1993) In another involving red deer, wapiti and F1 hybrids, the efficacy against adult Ostertagia-type ranged from 88%->99% (based on geometric means (GM)) (84-97% on arithmetic means (AM)) and against EL4's over 97-99% (GM-based) (96-99% AM-based) (Waldrup et al 1997)

It appears from this that albendazole at 10 mg/kg is only moderately effective against lungworm in red deer, ineffective in wapiti and probably somewhere in between with hybrids It is more consistently effective against abomasal parasites The differences are probably attributable to differences in the pharmacokinetics of albendazole and its metabolites between red deer and wapiti

(Waldrup et al.1997) Even in red deer, the data suggest that a higher dose rate would be required to achieve high efficacy against lungworm and stresses the importance of not under-dosing these animals. How this drug behaves in other deer species such as fallow appears to be unknown, It is interesting to note that a dose-rate of 7 5 mg/kg, it was ineffective against gastrointestinal nematodes in fallow as judged from a faecal egg count reduction test, although the reasons for this were unclear (Mylrea et al. 1991)

Fenbendazole

Fenbendazole has also been widely used on deer farms for many years – about 18% of 130 red deer farms and one of eight fallow deer farms in 1981 (Mason & Gladden 1983) Only one of the 16 farms studied by Audigé *et al* (1998) was using fenbendazole and then in the form of a combination with levamisole [which has poor efficacy in deer] The recommended dose rate is 7 5 mg/kg

Published information on the efficacy of fenbendazole in deer is again very scanty Overseas observations mostly relate to range deer of various species given the drug in feed for various periods of time (e g Duwel *et al.*1979, Kutzer & Prosl, 1979) Mason (unpublished, in Mason & Beatson 1985) concluded from preliminary work that it was highly effective at eliminating the shedding of lungworm larvae Further studies supported this (Mackintosh *et al* 1984, Mason & Beatson 1985). 100% of treated animals were found to be still not shedding larvae 21 days after treatment suggesting that the drug removed both adult and larval lungworm However, I have been unable to find any slaughter trial data to confirm this

Surprisingly, I was also unable to find published data on the efficacy of fenbendazole on gastrointestinal nematodes in red or fallow deer under New Zealand deer farm or similar conditions While it is highly likely that fenbendazole is highly effective against at least adult GI nematodes in deer, and overseas studies such as those mentioned above would certainly support this, the lack of good data is not helpful. There is evidence that fenbendazole administered in feed at 15 mg/kg given over five days was not effective against inhibited (hypobiotic) EL4 *Ostertagia*-type nematodes in red deer (Connan 1997)

Oxfendazole

This has been by far the most widely used BZ for deer for many years with over 50% of the farms surveyed in 1981 (Mason & Gladden 1983) and 13 of 16 (81%) of farms surveyed in 1992-4 by Audigé *et al* (1998) Given its well-established potency and popularity for use in other ruminants this is, perhaps, not surprising From the earliest trial work, indications were that at the recommended dose rate of 4 5 mg/kg, it was very effective at reducing the shedding of lungworm larvae to very low levels (Mackintosh *et al* 1984, Mason & Beatson 1985, Bowie *et al* 1987, Mackintosh *et al* 1990; Parsons *et al* 1994). Most animals have been found not to shed larvae for about three weeks after dosing, suggesting successful removal of adult and larval lungworm (Mason & Beatson 1985; Bowie *et al.* 1987; Mackintosh *et al* 1990) However, in most trials, larval excretion was not totally eliminated in all animals even, in some cases, with double or repeat dosing (Mason & Beatson 1985; Watson 1986, Bowie *et al* 1987) Again, no data from slaughter trials appear to be available

Although the effect of oxfendazole on lungworm infections has been examined in a number of trials, there is an almost total lack of data on efficacy against gastrointestinal nematodes. As one of the most potent BZ's, it would be expected to be effective, at least against adults and later larval stages, and there may be some unpublished data somewhere!

It has been shown that oxfendazole is more rapidly metabolised by red deer than by sheep (Watson & Manley 1985). Since the same dose rate is recommended for sheep, cattle and deer, one cannot help wondering if that dose is optimal for deer, and whether all deer species are all the same in that respect At least one would suspect that there may be little or no margin for under-dosing without the risk of significantly affecting efficacy.

Macrocyclic lactones – the avermectin-milbemycin group

Ivermectin

Ivermectin was the first of this group to become available and it had an immediate impact on parasite control in deer It is interesting to note that there are more publications on ivermectin in deer than on any other anthelmintic As ivermectin for cattle was not available before 1982, it does not feature in the survey carried out that year (Mason & Gladden 1983) but it was being used on 7/16 farms studied in 1992-94 (Audigé *et al.* 1998) On three of these it was the oral formulation alone that was being used over that period, on the others either the pour-on formulation alone or both oral and pour-on on different occasions In fact, it is only the pour-on formulation that carries a label claim for use in deer, not the oral or injectable forms although the latter has been used in a number of trials both here and overseas

Early trial work in New Zealand indicated that subcutaneous injection of ivermectin at the standard recommended dose of 200 µg/kg was highly effective in eliminating shedding of lungworm larvae for at least three weeks after treatment (Mackintosh *et al* 1984, Mackintosh & Mason 1985; Mackintosh *et al.* 1993) The same dose rate given orally was also highly effective in reducing faecal larval counts (Mackintosh *et al.* 1984) A further trial using both oral and injectable ivermectin again showed high efficiency against larval shedding, although low level larval excretion continued in a few treated animals; it also appeared that the ivermectin treatments provided some persistent effect against lungworm (Bowie *et al.* 1987) Two slaughter trials carried out in New Zealand have shown total removal of both immature and mature lungworm by 200 µg/kg given by injection (Mackintosh *et al* 1985, 1993)

The development of the pour-on formulation of ivermectin provided an alternative and, particularly for older animals, a more convenient approach to treating deer. Trials have shown that at a dose rate of 500 µg/kg, not only is treatment highly effective against *Dictyocaulus* (Mackintosh *et al* 1990) but that there is a persistent effect that protects against new infection for at least 28 days (Rehbein & Visser 1997)

There is less information on the effect of ivermectin on gastrointestinal nematodes, the focus having been primarily on lungworm A slaughter trial carried out in New Zealand showed that a subcutaneous dose of 200 µg/kg removed virtually all the lumenal stages of *Ostertagia*-type and *Trichostrongylus* abomasal nematodes and about 85% of the larvae in the mucosa (Mackintosh *et al.* 1993). However, workers in the UK consider that a dose of 200 µg/kg is not adequate since faecal egg counts can reappear after only two weeks (i e within the prepatent period) indicating incomplete removal of larvae; they recommend 400 µg/kg as the dose to use with the injectable formulation (Andrews & Lancaster 1988, Andrews *et al* 1993) At this higher dose rate, injectable ivermectin has been shown to remove virtually 100% of adult and developing abomasal nematodes and >95% of inhibited (hypobiotic) EL4's from red deer (Connan 1997)

As far as I can find out, nothing has been published on the efficacy of the pour-on formulation on gastrointestinal nematodes in deer Given its effectiveness against lungworm and the data on the injectable form, it is reasonable to assume that it would be effective but just how effective is unclear and some data would be useful.

There is little information on the effectiveness of ivermectin in fallow deer In a Faecal Egg Count Reduction Test in Australia, an oral dose of 200µg/kg was found to only reduce egg counts by only 43% (Mylrea *et al* 1991). It appears that the pour-on formulation has been used in fallow deer in Germany but the paper is not readily available and the abstract provides little information beyond the comment that treatment at six week intervals kept lungworm larval counts at undetectable levels (Rehbein *et al* 1993)

Studies of the pharmacokinetics of ivermectin in red deer following injection (Mackintosh *et al.* 1985, Lancaster & Andrews 1991, Andrews *et al* 1993) have shown that there is wide variation

between animals and that the peak levels reached in plasma are considerably lower than in cattle. It was suggested that this might account for the reduced efficacy observed in their trial (Andrews *et al.* 1993) It also raises the question as to how the drug behaves in other species or sub-species of deer and whether this could affect efficacy I have not found any data on the kinetics of ivermectin after topical application to deer

Eprinomectin is also marketed for use as a pour-on for deer but I have not found any data on its efficacy that is accessible Given its efficacy in cattle, it could be expected to have similarly high efficacy in deer but no details are available

Moxidectin

Following the introduction of moxidectin pour-on, two trials were carried out on red deer weaners involving both faecal examinations post-treatment and slaughter of a sample of animals These showed that it was highly effective against both lungworm and gastrointestinal nematodes at the standard dose rate of 500 µg/kg (Mackintosh *et al* 1993, Middleberg 1994) Faecal egg and larval counts were reduced to zero in almost all animals in a few days and there was total removal of lungworm and 99% of adult and larval GI nematodes A trial comparing efficacy in red deer with wapiti hybrids indicated similar activity in both (Waldrup *et al.* 1998). A controlled trial with penned animals also showed that moxidectin pour-on prevented the establishment of challenge infections with both lungworm and gastrointestinal nematodes for at least 42 days after treatment (Mackintosh *et al.* 1997). Whether this length of protection is achieved consistently under field conditions does not appear to have been investigated

Abamectin

Although abamectin pour-on has a label claim for gastrointestinal and lungworm in deer, I have been unable to locate any published trial data One cannot simply assume that it is equivalent to the other two in this group. The label claim is for larval and adult lungworm, *Ostertagia*-type nematodes and a number of other named gastrointestinal nematodes, there is no claim for extended activity. Presumably there are some trial data somewhere!

Discussion

It has to be said that while one can accept that carrying out trial work to establish the efficacy of anthelmintics is expensive, it is disappointing to find so little efficacy data relating to deer of any kind and farmed deer in particular It should also be said that much of what has been done in relation to farmed deer, has been done in New Zealand but, even so, there is not a lot of it and there are very considerable gaps One must then ask if the fact that so much has to be taken on trust and that we routinely recommend and use anthelmintics in deer with so little information to go on is a cause for concern and, if so, to what degree

No doubt opinions would differ about this and some would argue that the experience gained from the use of the anthelmintics we are concerned with under field conditions, in many cases over many years, more than makes up for any lack of hard data from trials The snag with this contention is that it presumes objective assessment of the effectiveness of treatments given and that is, I imagine, rarely carried out There is no question that, in most circumstances, the drugs available will, with one possible exception discussed below, effectively prevent clinical disease and promote satisfactory growth rates. And, after all, we are not trying to produce worm-free animals. However, I would suggest that while experience of parasite control can, in spite of the lack of data, provide a measure of confidence, there is sufficient evidence available to indicate that one should not assume too much and that there are some issues that warrant thinking about

But perhaps before going further into that, we should consider briefly what the objectives of using these anthelmintics are

A primary consideration is parasite control in young deer in the post-weaning period with the aim of preventing clinical lungworm disease and minimising subclinical effects of lung and gastrointestinal

parasitism. The usual recommendation is for regular treatments at intervals short enough to prevent pasture contamination over the late summer/autumn period when larval populations would be expected to peak and when obtaining good growth rates is of critical importance It is worth noting that a recent study indicated that the treatment intervals used were often longer than would be considered ideal (Audigé *et al* 1998) At this age deer are usually of a size that they can be handled relatively easily so that administration of oral preparations is not generally a problem

The same study suggests that anthelmintics are also widely, if variably, used in older animals, particularly yearlings and adult stags although the rationale and benefits of this are uncertain and open to question (Wilson *et al* 1997, Audigé *et al* 1998) This seems to me to be an important area for investigation as using anthelmintics for no good reason is to be avoided

From the limited information available, it would appear that all three of the benzimidazoles currently marketed for deer will do an adequate job against *gastrointestinal* nematodes However, the relatively poor efficacy of albendazole against lungworm, even in red deer but more especially in wapiti and red/wapiti hybrids, indicates that this drug should not be relied on for lungworm control The other two BZ's appear to be more effective and consistent against both and the popularity of oxfendazole over the years is probably well-founded Nevertheless, one could be more confident about that if there were some slaughter trial data to back it up[1]

In addition, from what we know about the ability of deer to metabolise anthelmintics, and its variability between individuals, sub-species and probably species, it is critically important to ensure that animals are not under-dosed with BZ's if good efficacy is to be achieved Under-dosing can also encourage selection for drench resistance It is said that the weights of sheep and cattle are quite often under-estimated when animals are to be drenched No doubt this also occurs with deer and needs to be avoided.

Obviously, the avermectin-milbemycin (ML) anthelmintics, particularly the pour-on formulations which have a label claim for deer, offer several advantages over the BZ's For two of them at least, there is evidence of a high degree of efficacy against both lung and gastrointestinal parasites, persistent activity which allows longer intervals between treatments in a drenching programme and, of course, for all three the convenience of applying a pour-on to older animals that are less easily handled As indicated earlier, precisely how abamectin rates is unclear Here again, however, under-dosing is something to be avoided, not least because of the likelihood of reduced efficacy but also because of the possibility of under-dosing encouraging the emergence of drug resistance.

For all their advantages, and questions of relative treatment cost aside, in my view it would be a mistake to abandon the BZ's simply because they are, in some ways, 'outclassed' by the ML's or less convenient to use They both have their virtues and vices and I suggest that we need to be thinking about how we can ensure that both groups remain useful for as long as possible.

As far as I know, there have been no reports of anthelmintic resistance developing in nematodes of deer – probably more a reflection of the fact that no-one has looked for it than anything else But inevitably, sooner or later, it will emerge I suggest that we need to be thinking about it now and should be on the lookout for it by periodically checking the effectiveness of drenching, especially in young animals There are some particular difficulties in developing strategies to deal with this in relation to deer. I do not propose to discuss these in detail here but here are a couple·

1. Our almost total lack of information on the epidemiology of deer parasitism
2. The fact that the combination drenches that we would recommend for use in sheep and cattle to stave off the development of resistance contain levamisole which is of low efficacy in deer This would largely negate the beneficial effects of using them in deer.

There is an interesting question that arises in relation to anthelmintic resistance On farms where yearling and adult deer are given anthelmintic treatments as well as weaners, if BZ's are used in the post-weaning period, might there be some advantage (or disadvantage?) in using ML's in the older

stock This is something that would probably lend itself to computer modelling – if only we knew enough about the epidemiology of parasitism in deer to construct a model!

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