Resistance to chemotherapy: What are the risks for the reindeer industry?

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Introduction

In the last 50 years there have been some remarkable developments in the control of both internal and external parasites of domestic livestock by chemotherapy. These drugs offered very high levels of efficiency against a range of parasites, they were usually relatively cheap and were safe to use. They involved the so called 'second generation insecticides' such as DDT, the organophosphates and chlorinated hydrocarbons and for nematode control the benzimidazoles and the levamisole/morantel group of anthelmintics. Recently the avermectin class of compounds have been released which have extraordinarily high levels of efficacy against a whole range of arthropod and nematode pests.

However, the total reliance on chemotherapy to control these pests is now becoming threatened. Public attitudes are hardening against the intensive use of these drugs from an environmental and human health standpoint, and also the effectiveness of these drugs is now in jeopardy because of the emergence of drug resistant strains. These issues, particularly the latter, are now critical in the sheep industry of Australia. Considerable research has been carried out in this country to determine the importance of various factors in the selection of anthelmintic resistance in nematode parasites and on ways of limiting its spread, and on methods to overcome the problem. These principles are similar for any host/parasite system where parasite control is sought primarily by drug treatments, and thus includes the reindeer industry. Although no drug resistance has been reported so far for parasites of reindeer, it would be unwise to assume that this situation will remain the same indefinitely . It is important to consider the principles of selection for resistance and plan ways of limiting these so that the emergence of resistance can be avoided.

Biological aspects of drug resistance

There is a tendency to apply the principles and procedures established from research on insecticide resistance in arthropods to investigations on anthelmintic resistance in nematodes. Apart from the fact that both are metazoan organisms and that many resistant arthropods are important ectoparasites, the analogy breaks down. Unlike insecticide resistance, which occurs in a diverse range of arthropods and usually spreads rapidly to involve major geographic regions or entire industries, anthelmintic resistance is confined to a limited number of nematode species and has developed slowly with a patchy distribution. This may be attributed to:

Spatial mobility. The relative immobility of nematode parasites compared with insect pests and vectors ensures a delay in the spread of anthelmintic resistance. Migration is almost entirely dependent upon the parasitic stages within host animals and therefore the degree of livestock trading practised. However, when resistant worms are transferred from one farm to another, the parasites may lose their survival advantage unless similar selection pressure is

maintained. Also, on many occasions, animals from a farm or region where resistance exists are often moved to the slaughter house which obviously represents a «deadend» to the parasites as well as their hosts.

Restricted selection. Selection with an anthelmintic is imposed only on the parasitic phase within the host. In most circumstances, this represents only a small portion of the parasitic population. In other instances, stockowners treat only a portion of their flock or herd. This further reduces the overall selection pressure on the parasite population which is capable of existing in virtually all classes of hosts of the same species, all of the time.

Drug pharmacokinetics. The non persistent nature of all broad spectrum anthelmintics is also likely to have delayed the emergence of anthelmintic resistance. Rapid clearance of the drug ensures that the period of time during which parasites carrying resistance alleles enjoy a survival advantage over homozygous susceptibles is very short. The demise of a number of persistent insecticides, such as the chlorinated hydrocarbons, e.g. DDT, aldrin and dieldrin, was due to their slow degradation pattern.

Drug efficiency. A feature of all broad spectrum anthelmintics is not only their wide range of activity, but also a very high level of efficacy. To gain a market share, new drugs are expected to have an efficiency exceeding 90 %. This figure is frequently higher and there fore likely to retard development of resistance by restricting the genetic variability in the survivors of treatment.

Detection of treatment failures. Another likely reason for the delay in recognition and apparent non-uniform distribution of anthelmintic resistance is the greater difficulty users have in judging when treatments fail, compared with insecticides when a resistance problem is heralded by the clearly visible presence of survivors, or the early re-appearance of pests following treatment. In all animal production systems where the dominant parasites do not regularly produce acute clinical disease, resitance may go unnoticed and be more widespread than is commonly believed because farmers may not detect a reduction in animal productivity until resistance has reached a high level.

Development of anthelmintic resistance in the field

Currently available anthelmintics registered for use in ruminants can be calssified into two major classes based on their spectrum of activity, broad or narrow (see Table 1). Anthelmintic resistance is virtually confined to the broad-spectrum class, almost certainly because of the far greater use of these compounds. Within the broad-spectrum class, anthelmintics can be further divided into three groups, based on their chemical structure, mode of action and activity against resistant worm populations.

It has been commonly observed that resistance to one compound in a group within the broad-spectrum class, automatically confers some degree of resistance to other compounds. This is termed «side-resistance». Fortunately, there

Table 1. Commonly available anthelmintics for nematode control in ruminants

Broad spectrum:		
Group 1:	(Benzimidazoles and pro-benzimidazoles)	
	Thiabendazole	
	Parbendazole	
	Cambendazole	Thiophanate
	Mebendazole	Febantel
	Oxibendazole	Netobimin
	Fenbendazole	
	Albendazole	
	Oxfendazole	
Group 2:	Levamisole	
	Morantel	
	Pyrantel	
Group 3:	Avermectins	
Narrow spectrum:		
Group 4:	(Salicylanilides and substituted nitrophenols)	
	Bromsalans	
	Closantel	Disophenol
	Niclosamide	Nitroxynil
	Oxyclozanide	Brotianide
	Rafoxanide	
Group 5:	(Organophosphates)	
	Dichlorvos	
	Trichlorophon	
	Napthalophos	

are few cases of «multiple resistance» where parasites are resistant to two or more anthelmintic groups.

The factors which influence the rate of development and spread of anthelmintic resistance are outlined below.

Selection intensity. An important difference between selection for resistance in insects and in nematodes is that all stages of the insect population are commonly exposed to an insecticidal application, whereas it is only the parasitic stages of nematodes which are subject to selection by a dose of anthelmintic. If an anthelmintic is given when clinical signs of parasitism are apparent, usually there are large numbers of free-living stages on pasture which escape exposure to selection. In an initially susceptible population in these circumstances, the number of survivors following treatment with a modern broad-spectrum drug would be few, and their progeny would in turn constitute an exceedingly small proportion of the total free-living population.

If, on the other hand, anthelmintic treatment coincides with a period when the number of free-living stages are low or declining rapidly, then theoretically the progeny of the survivors would make a greater relative, but not absolute, contribution to the free-living population.

There is overwhelming evidence to link the occurrence of anthelmintic resistance with frequent treatment. If treatment intervals are close to the pre-patent period of the parasites, then the unselected free-living stages will have little opportunity to infect animals, to reach maturity and to produce eggs before the next treatment. If such a parasite control programme is maintained for an extended period, it is obvious that the entire population will be screened for resistant individuals and that these, if present, will inevitably increase in numbers, resulting eventually in a highly resistant population.

Under-dosing is also an important factor contributing to the development of resistance. To achieve maximum effectiveness from anthelmintic treatment, dose rates should be calculated according to the heaviest animal in the group. Unfortunately, it is a common practice for farmers to estimate the dose of anthelmintic on what they consider to be the average weight of animals to be treated. Other forms of underdosing are associated with faulty equipment or diluting anthelmintics with water or other substances.

An important strategy in preventing, or slowing the rate of development of resistance is to alternate between the anthelmintic groups. Current recommendations are for annual rotation, to prevent parasite populations being exposed to multiple anthelmintic selection within the same generation if rapid alternation was practised. However, alternation needs to occur to prevent resistance genes from accumulating within the parasite population. Many cases of resistance have emerged because farmers continuously used drugs within the same group, although they believed that by simply changing brand names they were achieving effective alternation. Unfortunately, what is frequently observed is that once drug failure is observed, resistance levels are high and there is little chance of reversion back to susceptibility after changing to another drug group.

Ecological factors. It is incorrect to assume that parasites which survive anthelmintic treatment will automatically contribute to the development of resistance in succeeding generations. It is expected that broad-spectrum anthelmintics will remove 95–99 % of a susceptible parasite population and if, for example, 10.000 parasites were present before treatment, this would be reduced to 100–500 survivors which would need to locate each other to produce progeny. Even if resistance is present, the breeding success of the post-treatment population may not be high because there is likely to be differential drug efficacy between the sexes and also because anthelmintic treatment may diminish egg production of female parasites.

An overriding consideration which determines the ability, or otherwise, of surviving parasites to remain *in situ* for sufficient time to produce resistant progeny, is the influence of host-induced effects that regulate the parasite population. Resistance could be expected to develop slowly if parasites which survived anthelmintic treatment were rapidly lost and replaced by a process of turnover as described for the bovine parasite, *Ostertagia ostertagi.*

Although the free-living stages of trichostrongylid nematodes provide the means whereby new hosts are colonized, they are not important for dispersal. Except in extreme conditions of rainfall run-off they do not migrate further than a few centimetres and they lack transport, or paratenic, hosts. The only way in

which resistant populations can be effectively disseminated is by movement of their hosts. This is an important distinction from insecticide resistance. Firstly, it is likely to have a bearing on the non-uniform distribution of anthelmintic resistance compared with insecticide resistance. Second, and far more important, it highlights the fact that the individual farmer is liable for his own anthelmintic resistance problem, whether he creates it himself or imports it with purchased stock. By contrast, if the individual farmer incorrectly uses insecticides this will have a widespread impact not under the control of more responsible users.

Control practices in relation to anthelmintic resistance

Single administration.

Single oral dosing is virtually the only method by which anthelmintics are administered to small ruminants (sheep and goats). This is due to the ease of using this procedure in these types of animals and the control the farmer has over the timing and volume of drug given to each animal. Disadvantages lie in the possible inaccuracies associated with poor technique and the failure to gather all animals under extensive grazing conditions.

Injectible formulations of anthelmintic have considerable appeal for anthelmintic dosing for cattle and of course for reindeer. Formulations of levamisole, and more recently ivermectin, for subcutaneous administration provide ease and safety of dosing in these classes of animals because head restraint is unnecessary.

Dermal application of levamisole has been developed only for cattle and the merino breed of sheep. In this method, the anthelmintic needs to be both lipid and water soluble to achieve rapid cutaneous absorption and there is certainly variable efficiency between breeds and seasons. Therefore there is a danger of sub-optimal dosing of anthelmintic occurring which is a potent selector for resistace.

Sustained or controlled delivery.

The rationale behind anthelmintic administration in this way is not only to remove damaging or potentially damaging worm burdens from animals, but also to prevent contamination of pastures with parasite eggs for considerable periods of time.

Methods can be either group administration, such as the inclusion of anthelmintic in feed supplements, blocks or drinking water, or single animal dosing using intra-ruminal sustained release devices.

For group administration, convenience and labour saving are obvious as individual animal handling is not required, but at the same time, intake is voluntary and there is a chance that some animals will ingest more than what is required whereas others will receive less. This chance of sub-optimal dosing will increase the hazards of selecting for anthelmintic resistance.

The chances of sub-optimal dosing are largely overcome when controlled release systems are used. These devices release drugs continuously or intermittently over periods measured in weeks rather than days. The desired release profile is one where maximum daily dose rates are reached very soon after administration and they remain constant until there is a rapid reduction in drug concentration following the exhaustion of the device. In principle these devices substantially increase the risk of selecting for resistance compared to occasional single treatment. However, if sequential administration is avoided, usage is restricted to limited periods, and if devices with a fast decay are used, they may not cause an acceleration in the rate of selection for resistance.

Future prospects

Although there appears to have been a steady stream of new anthelmintics onto the market place in recent years, the majority were additional compounds in existing drug classes. This is of little benefit from the standpoint of resistance because side-resistance within a drug class often rapidly develops. Over the last 25 years only four different chemical classes of broad-spectrum anthelmintics have appeared, namely, the benzimidazoles, levamisole, morantel (pyrantel), and the avermectins. It is highly unlikely that there will be any acceleration in the rate of commercial release of alternative, highly effective anthelmintics since the process from discovery through to marketing may take 6–8 years with costs exceeding $US 30 million.

Research and advisory workers in countries, or for animal production systems, where anthelmintic resistance appears at the present time not to be a problem, cannot afford the luxury

of considering that this is a concern only of others. Anthelmintic resistance will not disappear spontaneously, and must inevitably increase if the traditional methods of worm control continue to be practised. It is unrealistic to assume that the development and release of alternative, highly effective anthelmintics will keep pace with resistance to existing drugs. Nor can one be sanguine about the expectation that non-chemotherapeutic methods (such as worm vaccines) will resolve this problem in the short term.

It is doubtful whether control programmes which have anthelmintic treatment as a component can avoid selecting for resistance. However, if users of anthelmintics are made aware of the best ways to use these drugs to extend or maintain their effectivenes, this will allow more time to explore the possibilities of other methods of worm control.

Short-term behavioural responses of Svalbard reindeer to direct provocation by a snowmobile

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Summary: Short-term behavioural responses of 101 groups of Svalbard reindeer (*Rangifer tarandus platyrhynchus*) to direct provocation by a snowmobile were recorded in April (late winter) 1987. The median size of groups = 3.3 animals. Reindeers' first visible responses to an approaching snowmobile usually involved independent behaviour by different individuals in a group. Flight, by contrast, was a co-ordinated group response. Groups' median response distances were: minimum reaction distance = 640 m, disturbance distance = 410 m, distance at initial flight = 80 m and distance of flight = 160 m. Groups' median response times were: total running time = 22 s, total locomotion time = 38 s, maximum duration of disturbance = 193 s. Energy and time budget models indicate that one median flight response can cause an increase in a reindeer's daily energy expenditure (DEE) of approximately 0.4 % and a loss of daily grazing time (DGT) also of 0.4 %. Corresponding values for one maximum and one minimum flight response are 4.7 % and 0.01 % of DEE and 4.6 % and 0.03 % of DGT, respectively. The rate of disturbance of reindeer by normal snowmobile traffic, measured during 24 h watches of groups of animals, was one disturbance per group per two days. Reindeer which were disturbed by normal traffic walked away slowly but never ran at all during this series of observations.

This study, which considered only reindeers' immediate, overt responses to provocation and which purposely ignored all psychological and physiological aspects, failed to detect any way in which the current level of snowmobile traffic might substantially reduce the physical well-being of Svalbard reindeer. This surprising conclusion is based principally on consideration of the low frequency with which the animals are overtly disturbed by normal snowmobile traffic together with the short duration of their response to disturbance. Clearly, also, there is no reason to expect Svalbard reindeer to respond to provocation in the same way as other subspecies of *Rangifer*. Caribou or continental wild reindeer live under constant threat of suddenly having to gallop off from biting flies, wolves, hunters etc. Having to escape from things in a hurry is part of their daily life; for Svalbard reindeer this is not the case.