PRESIDENTIAL ADDRESS 1994

Anthelmintic resistance in the New Zealand Animal Production Industries

T.G. WATSON

AgResearch, Ruakura Agricultural Research Centre, Private Bag 3123, Hamilton, New Zealand.

Early modern anthelmintics were developed with broad spectrum activity to eliminate the major production limiting round worm parasites from farmed ruminants. These original chemical therapeutics fell into 2 'action' groups, white drenches (benzimidazoles) and the clear drenches (levamisole and morantel). All members of each so-called group or family have common distinctive action on the parasites. There may be subtle differences in effectiveness between members within each of the two families, but modes of action within groups will remain the same. This is important to know, particularly when assessing the effectiveness of drenches.

Members of the benzimidazole group actually kill the worms by effectively starving them of nutrients (Table 1). All members of this group kill various stages of the parasites including the egg.

TABLE 1: Some of the anthelmintic products available in New Zealand.

Group 1 White	Group 2 Clear	Group 3 Milbemycin Avermectin	Group 4 Combination
Albendazole	Agmax Gold	Cydectin	Arrest
Albezol	Bayer	Ivomec	Crusade
Axilur	Armagold	Vetdectin	Dual-Atak
Bayer	Citarin L		Justice
Armadrench	Endex Sheep		Leviben
Fenben	Exhelm-E		New Arrest
Nufarm	Levasole		
Nemadet	Levicare		
Oxfen	Levitape		
Paladin	New Levitape		
Panacur	Nilvax		
Rintal	Nilverm		
Rycoben	Nilvet		
Synanthic	Nilzan		
Systemex	Nufarm Lev		
Telmin	Ripercole		
Valbazen	Rycozole		
	Vermatak		

On the other hand the clear anthelmintics, products with levamisole or morantel, affect the movement of the parasites inducing a rigid paralysis with the result that the worms are 'flushed' down the gastro-intestinal tract (Table 1). Activity is generally restricted to various active, feeding stages and eggs remain unaffected passing into the environment to develop eventually into infective larvae.

During the last decade a third action group, the avermectin/milbemycin group, has been developed and registered for use in a wide variety of animals including sheep, cattle, deer and goats (Table 1). Developed as the first 'endectocide' within this group, ivermectin has activity against not only the round worms, but also various external parasites. This break-through has been followed more recently with the milbemycin, moxidectin and the yet to be released avermectin, doramectin. All three have now been classed as avermectin/milbemycins with similar activities and properties. Although activity comes by way of flaccid paralysis of the parasite this mode of activity has an entirely different basis to that of the clear drenches.

Another development in recent times has been the emergence of combination products (Table 1). There is some controversy over whether they represent a separate group because the members are characterised by a formulation which includes both benzimidazole and levamisole. Adding to the confusion is the fact that researchers including ourselves have noted that this group of products has afforded increased efficacy or some control of multiple resistances involving both white and clear anthelmintics. A synergistic mechanism has been postulated however the mode of activity has not been identified nor has the life expectancy of such products when used to control this type of resistance.

There are certain difficulties inherent with this user friendly classification of the various action groups. It was developed to simplify recognition for producers however with growth of product and formulation numbers it is now a fact that white drenches are not white and all the clear drenches are not clear. Furthermore, ivermectin and its newer relatives are clear. So with this confusion it is absolutely essential that labels be read carefully to know exactly what active ingredient is used in any product.

Drench resistance has now emerged as a major threat to animal production in New Zealand. Parasites develop resistance to drenches for a variety of reasons, but it is closely associated with prolonged and frequent use of any members of a single drench family. By definition, in any given parasite population some individuals will be able to remain unaffected by a dose of anthelmintic that would normally be expected to kill all of the worms. Any that survive exposure to this therapeutic level of drug may be considered resistant.

Resistance was first identified as an emerging serious problem on numerous sheep and goat farms in New Zealand as a result of surveys published after 1980 (Kettle *et al.* 1981 & 1983). Since then, there have been numerous accounts originating from various regions of the country of anthelmintic failure in sheep, goats and more recently, cattle. Many of these

were shown to be cases of drench resistance. At this stage it is likely even more cases have been diagnosed given the direct involvement of private veterinary practitioners. Commonly, the contributing factors in many cases have been: high frequency of drenching, prolonged use of members of one drench group, use of drugs from various families within the same year and improper dose rates. Resistant worms continue to infect the animal, shed eggs into the environment and depress animal health and production.

In New Zealand, the most significant cases of anthelmintic resistance have been detected in the goat industries. Furthermore, this is the case throughout the world. Resistance by nematode parasites infecting goats has now been reported from goats in Australia, Belgium, France, India, Kenya, New Zealand and the United Kingdom. A recent case of ivermectin (IVM) resistant worms having been isolated from Angora goats in quarantine in Slovakia following shipment from New Zealand illustrates the international importance of the phenomenon (Varady *et al.* 1993; Varady *et al.* 1994).

Reports of resistance on goat properties in this country were first documented following a survey of milking herds (Kettle, Vlassoff, Reid and Horton 1983). At that time, of 47 herds tested, 74% had resistance to BZ drugs, 42% to levamisole (LEV) and 38% had resistance to both families. IVM was released for use only in cattle in 1982 so was not tested. A more recent survey focused on 10 goat properties in the Manawatu. Scherrer *et al.* (1989) revealed that 90% had BZ resistance but IVM failure was not detected. The study did not investigate LEV so properties with LEV and/or BZ/LEV resistance were not recorded. The faecal egg count reduction test (FECRT) was used in both surveys. This test simply records change of faecal nematode egg count (FEC) before and 7-10 days after anthelmintic application. Between the two studies the criterion for defining cases was increased from <80% to <90% reduction. This just applied more sensitivity in line with limits set in more recent times. All major parasites including *Haemonchus*, *Trichostrongylus* and *Ostertagia* have been implicated.

To date, published reports of IVM resistance by worms in goats have been restricted to 4 cases (Badger and McKenna 1990; McKenna *et al.* 1990; Watson and Hosking 1990a; Pomroy *et al.* 1992). Controlled experimental dose titration studies have been conducted in lambs using one strain. Level of resistance required that approximately eight times the recommended therapeutic dose rate to be given to reach the efficacy expected of the drug (Watson and Hosking 1990b). Further *in vitro* titration studies showed resistance to ivermectin had developed to twenty-three times the normal recommended dose rate (Shoop *et al.* 1993).

There are indications that documented cases of IVM resistance (and BZ or LEV for that matter) may make up just a very small fraction of the numbers currently present on farms. Aside from the 4 published cases there are many other anecdotal reports of resistance. No other surveys have been documented. In fact, none have been undertaken because of cost, $200-$900 per farm. Most additional published information arises from isolated reports and studies of various strains. Detection of resistance has been reported from different parts of the country but generally many producers remain silent after noting failure of animals to thrive following treatment. Veterinarians are also diagnosing many cases which are not being reported. Much is unsubstantiated, spread throughout the industry in casual conversation. Our laboratory has been involved in demonstrating cases on dairy and fibre goat industry properties. Multiple resistance involving IVM and BZ has been recorded in almost all cases investigated to date. Producers, themselves are aware of or suspect various types of resistance including IVM in goats (and sheep) held on various quarantine stations throughout the country. All breeds are at risk.

Wherever IVM has been used at high frequency to the exclusion of other anthelmintics for some time (possibly as short as 3-4 years) problems may be expected. Anthelmintics have been abused by farm managers and producers for many years. Much of the industry has already lost the effective use of many of the modern broad-spectrum anthelmintics already and it doesn't appear they have learned. Despite manufacturer claims that their new milbemycin product, moxidectin (Cydectin, Vetdectin), will control IVM resistance side resistance between the products within this group can be expected. It is simply a modified form of IVM. Moxidectin (MOX) has not (**and hopefully will not**) be registered for use in goats (Kieran 1994). Despite this, farmers and farm managers have begun to use it to control parasites in sheep and goats. Even more worrying, veterinary practitioners are reported to be recommending its use in these animals and in such incidences one must suspect that IVM resistance may be behind adoption of the product. "Off-label" use of a cattle formulation has been implicated with deaths of over 200 ewes on the South Island. Registration for use of the product in sheep has yet to be finalised by the Animal Remedies Board. Side resistance within the avermectin/milbemycin group was demonstrated almost 2 years ago using an original IVM-resistant isolate (Watson 1992, unpublished report). The issues are far from simple. Under field conditions MOX was shown to be completely effective against IVM-resistant *Ostertagia* (Pomroy *et al.* 1992; Watson and Hosking 1993). It appears that dilution of the resistant population by susceptible forms continues to make diagnosis in the early emerging stages difficult in the field. Recently, reduced efficacy of MOX in another strain was confirmed in experimental studies conducted indoors (Pomroy and Whelan 1993). The problem will not simply disappear. Genes for resistance would be expected to remain in the parasite population until the population itself dies out. Spelling and cropping for 1-2 years has not been successful at least in one case and gradual or spontaneous reversion to susceptibility is highly unlikely. **This means resistance may be established forever.** But there appears still to be some flexibility and opportunity cannot be ignored. IVM resistance has been monitored at 2-3 sites over the last 3-4 years. Effective animal, pasture and anthelmintic management and programming of therapeutic application appears to stabilise IVM resistance however it remains easily detectable (Watson and Hosking 1993).

The significance of anthelmintic resistance to the sheep and goat industries in New Zealand rests in the dramatic effects uncontrolled parasitic disease have on animal survival, management and production. It has been estimated that between 20-40% of sheep production may be at risk. Even though milk must be withheld after anthelmintic application

crude estimates from research studies would suggest that use of effective anthelmintics could account for a response in the order of 30-50% in dairy goat production (Watson unpublished). On this basis, it is reasonable to suggest that similar values may be applied to goat fibre production although no data have been reported. The fibre industry may be in disarray but dairy goat products are finding important markets in Asia with export earnings of $6 million projected for 1993-94. The dairy industry has aligned itself to the NZDB to identify and prospect markets. This segment of the goat industry will require research funding support in addition to what the industry itself can provide. The dairy sector has already demonstrated their commitment with research funding. I am not convinced the fibre industry will be in the same position even in the medium term.

There are major implications for farming other animal species arising from the resistance situation in which the goat producers now find themselves. At issue is the viability of mixed, alternate or integrated intensive grazing and animal management systems which have been developed, recommended and adopted during the last decade. Complementary stock are used under these farming practices to control or prepare pasture and anthelmintics are used or required strategically to control parasites.

The greatest potential impact could be felt by the sheep industry because all strains resistant in goats will readily cross-infect to sheep. Resistance to anthelmintics by nematode parasites was first reported in sheep in New Zealand (Vlassoff and Kettle 1980). Cases of IVM resistance in sheep have been reported in Brazil, and South Africa while unsubstantiated rumours are circulating that a case (it would be the first) has been identified in sheep in Southland. Surveys of sheep farms on the North Island have suggested that we can expect approximately 65-70% of properties to have problems with resistance. By far, the white drenches are the most endangered group but there is some indication that resistance to levamisole may be on the rise. This is probably a consequence of increased use and reduced price that have occurred at the same time as benzimidazole use has declined after detection of resistance. IVM resistance has yet to be detected on sheep properties where goats have not been farmed.

There are indications that the cattle industry is heading down the same track, albeit at a much slower pace. A small number of incidences of white drench resistance have been diagnosed or reported. Some species naturally infecting sheep and goats may cross to cattle but this has not been demonstrated with any resistant strains to date. Resistance to benzimidazoles by cattle parasites was first detected in 1987 (Jackson *et al.* 1987). Since then approximately 6-10 more have been detected. Currently at least one clinical investigation has focused on a potential multiple resistance from cattle implicating an avermectin and a benzimidazole (Watson, unpublished). Resistance to avermectin/milbemycin products has not been published however surveillance has been extremely limited and has not monitored efficacies despite the fact that many cattle producers used benzimidazoles prior to 1981 when ivermectin was first marketed for cattle. Because of the stock value, ease of application and drug efficacy many producers have used this latter therapeutic almost exclusively. In real terms, this means that there has been over 20 years of selection for benzimidazole resistance which has been followed by almost 14 years of selection pressure applied to ivermectin.

Some of the most important issues facing producers, processors and producer boards as we approach the next century are the uncertainty of markets, stability of prices and quality of product. At the same time, one of the most important problems facing producers, researchers, clinicians and farm consultants is formulating a system designed to limit input requirements for ruminant farming yet maximise and sustain efficient productivity with effective management of animal health. In particular, I would suggest that control or management of parasites has become a major concern that remains unresolved and is intensifying in complexity because of confusion and often ignorance from many quarters. It would appear that the problem is not one of producer awareness but rather a question of poor definition and lack of uniformity in interpretation and views on how to overcome difficulties.

Increased focus on parasites has meant increased numbers of researchers and consultants keen to capture dollars when survival was measured in terms of salaries, operating funds and the inevitable overheads. Much of the producer board funding made available has tended to have a direct farmer focus emphasising extension or transfer of technology in a consultative manner. Monitor farms and parasite action groups have been developed for this role as short term 'visible' efforts designed to define management systems while resources targeted for long term studies have been in the genetics of resistance or tolerance to infection. Both short and long term approaches have profile in the farming and research communities. Public Good Science funding has been directed toward more basic and long term projects in strategic areas which may or may not show a benefit to the industry such as immunology, genetics, molecular biology, and computer modelling. Even though anthelmintic resistance may have been the catalyst, current direct research in the field appears to be almost nil. It seems to be reliant almost entirely on extension initiatives and despite the wide gaps in our understanding of the phenomenon everyone seems to have become an expert.

Many sheep and cattle producers remain unconvinced that resistance will be a major issue in the long term because of an expectation that new products will be introduced and the difficulty that production losses are not being detected. Their apathy is further strengthened by the inconclusive scientific evidence currently available as well as the inconsistency of interpretation and recommendations by technical representatives, veterinarians, researchers and consultants alike. Until there is sound evidence to support the expectations that resistance is or has become an important production limiting animal health concern the majority may continue to believe it will be "their neighbour's problem". As one of the more stable, dependent and progressive segment of the agricultural community, sheep and beef farmers should be able to learn from their goat producer counterparts before they too are confronted with widespread multiple resistance.

The majority of fibre and dairy goat producers have been convinced of the impact resistance will have on production dollars. There are obvious ways of delaying resistance emerging but control, management and elimination of resist-

ant strains after their emergence may not be a simple task that can be identified or adopted by each and every producer. This insidious problem takes considerable time to manifest and as a result is difficult to diagnose. It is governed by many environmental, animal management and genetic selection pressures that are not clearly defined.

The lack of widespread multiple resistance in the sheep industry has been brought about by the ability of these stock to develop a strong host immunity, by the relaxation of drenching pressure through various animal and pasture management procedures that support controlling parasites and the low product value in the face of high endectocide costs. In the beef industry, high product value has offset high endectocide costs by easy injection and pour-on applications as well as superior anthelmintic efficacies. However, financial and product marketing considerations have tended to cloud issues as new products or delivery systems have been introduced. Lack of information has not helped predict the longevity of effectiveness for the new arrivals but market share has obviously been a factor in marketing information disclosures and strategies in recent times. On one hand we see the technical representatives from drug companies advocating policies to reduce application frequencies to lessen the impact on selection for resistance whereas marketing reps use production advantages to demonstrate the value of increased treatment frequencies or extended release delivery systems.

Despite the vagueness of the situation and complexities of the issues producers should not become complacent. There is some evidence that although early detection is difficult and inaccurate given the current techniques things are changing. Genetic markers for anthelmintic resistance in nematode parasites are being investigated and will assist to identify resistance when gene frequencies are low. Early, detection will assist to develop effective parasite control procedures that will help minimise the impact nematodes have on productivity and animal health. At the same time, measures may be adopted to reduce the risk of translocation between properties and develop system approaches to animal farming for parasite management and control.

In conclusion. it is critical that producers take steps to delay or avoid resistance.

There are no new action families on the horizon. Resistance to white and clear drenches has been diagnosed in parasites of sheep and goats and ivermectin/moxidectin-resistant worms have been isolated from goats. Although levels and types of anthelmintic resistance on goat properties have not been surveyed in recent times they are probably considerably worse than those predicted for sheep. Results of FECRT in various parts of New Zealand suggest that about 65% of sheep properties may be experiencing some form of white drench resistance. Because many goat nematode parasites will readily infect sheep they represent a very serious threat to effective parasite condition in the sheep industries.

Finally, use of the newer close relative, moxidectin, in goats will only maximise the threat in the longer term given both have been developed from a similar parental chemical compound. It is not registered for use in goats. Current recommendations for its use in goats by some veterinary practitioners, clinicians and advisers must be avoided at all cost.

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