Welcome to this issue of TTW. The main purpose of this informal newsletter is to share information with those particularly interested in the management of endoparasites of farmed animals, including sheep, goats and cattle.

DRUG RESISTANCE IN FASCIOLA HEPATICA

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Aspects of resistance in liver fluke are discussed, partly in light of work we carried out at the Elizabeth Macarthur Agricultural Institute (EMAI) of NSW DPI.

A survey was conducted by Boray and others between 1989 and 1991. It was shown that about 60 % of the endemic properties had a degree of resistance to rafoxanide and closantel against flukes aged 6 weeks, but the flukes were susceptible to the drugs when the flukes reached their adult stage, 8 to 10 weeks after infection (Boray and De Bono, 1989). Further tests showed that the combination products were effective against...
immature resistant flukes if the treatment was carried out with a combination product containing closantel and oxfendazole, through synergistic action (Rotafluke®, Closicomb®, Boray and Sluyter, 1997).

The problem with triclabendazole resistance is more difficult because, when resistance develops, the drug does not kill flukes at any age from 2 weeks to 12 weeks old (Boray et al., 1997). Triclabendazole-resistant flukes are widely distributed in the Goulburn Valley irrigation area in Victoria and a laboratory selected strain, originating from a property in the NSW central tablelands, showed total resistance to triclabendazole after challenge with the drug (Walker et al., 2004).

As to the benzimidazole carbamates, trials conducted at EMAI showed some have some activity against liver fluke, but only against the adult stages. Of the BZs, luxabendazole (Hoechst) has the highest activity, but unfortunately commercial production of this drug had ceased. In our trials the drug was effective against immature flukes as well and its efficacy in combination with triclabendazole or other flukicides against immature flukes was high. Amongst the rest of the BZs, oxfendazole showed good efficacy against liver fluke aged 16 weeks or older. The combination products of triclabendazole and oxfendazole demonstrated good synergistic action and high efficacy against immature flukes (Flukazole C® for cattle and Flukazole S® for sheep). Further data on synergistic combinations can be found in Fairweather and Boray (1999).

In our sheep trials (AT84), a reasonably good synergism was demonstrated against a triclabendazole resistant fluke strain. In Victoria a very serious resistance is slowly spreading south from Pyramid Hill, and the use of a synergistic combination offers good control. The combination of oxfendazole and closantel showed good synergistic effect with high efficacy against a closantel resistant fluke strains.

On dairy farms only ivermectin-clorsulon combinations can be used for lactating cows. Some of those products are cleared for that purpose. Those injectable combinations are more effective and better tolerated than the levamisole-oxyclozanide combination, or albendazole. Triclabendazole or the triclabendazole-oxfendazole combination can be given to young heifers, dry cows or pregnant cows up to 21 days before calving.

REFERENCES


STRATEGIC CONTROL OF FASCIOLOSIS CAUSED BY A VERY SOPHISTICATED AND RESILIENT LIVER FLUKE, FASCIOLA HEPATICA

An Essay for General Information

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Introduction

One of the most debilitating parasitic diseases of sheep and cattle in Australia is liver fluke disease. Graziers spend about $10,000,000 per year on fluke drenches alone and production loss may cause another $50-80,000,000 annually depending on seasonal conditions. The production of wool is reduced in quality and quantity and lambing rate is
lowered, the lambs have poor growth and replacement cost is increased. In cattle, fasciolosis causes reduced production and quality of milk, reduced growth rate and delayed conception rate in heifers (Boray, 1985, Dargie, 1986).

About 250 million sheep and 300 million cattle are potentially affected by the disease world-wide. The clinical disease is more often manifested as a chronic anaemia. However, we have to emphasise the important role of acute and sub-acute fasciolosis causing production loss and mortalities.

Control of fasciolosis is difficult and eradication is impossible in endemic areas without unsustainable expenses. The fluke survives in the host, in the snails and in the environment for long periods under good or unfavourable conditions. Apart from sensible farm management, only a strategic treatment programme, according to local climatic conditions, can keep the disease under sustainable control.

Survival of flukes in the final hosts

In sheep the fluke will survive and produce eggs as long as the sheep lives, if not treated. The longest infection in sheep after a single infection was recorded as 11 years. Even a single fluke in sheep may produce up to 50,000 eggs per day, contaminating the pastures where the intermediate host snails are present.

The fluke also survives for long periods in goats, domestic and feral pigs, kangaroos, wallabies, wombats and possums. Cattle and buffaloes have a natural resistance and a single infection will not survive longer than a year (Boray, 1969). Rabbits are susceptible to Fasciola hepatica and can maintain an infection for long periods but after a few passages the eggs of flukes are not viable. In the absence of other hosts the rabbit does not contribute to the contamination of pastures (Boray, 1969).

In the intermediate host snails

Three species of snails are now endemic in Australia, the indigenous Australian snail, Lymnaea tomentosa, which is dominant in Australia and New Zealand, and two introduced species, L columnella and L viridis. Unfortunately those introduced snails can thrive in permanent water sources at higher temperatures, while the Australian snail can only live in shallow creeks, springs and irrigation channels. The role of introduced snails in the epidemiology of fasciolosis has been discussed (Boray, 1978).

The reproduction of snails is continuous throughout the year but peak numbers of young snails emerge from spring to the end of autumn. The reproduction rate of snails is very high and, theoretically, one surviving snail can produce one million snails in sixty days under favourable conditions. The snails become infected by the larvae of flukes, which hatch out from eggs (miracidia), and subsequent larval stages rapidly multiply within the snails. One single miracidium may produce 4,000 infective larvae (metacercariae).

The snails may survive in drought under the mud for more than a year and the fluke larvae also survive in the snails for long periods, but stop developing and resume development after rain. In winter the snails survive in Australian climatic conditions in the endemic regions and the fluke larvae survive within the snails but stop development until the spring. At the increase of temperature the larvae rapidly develop into the infective stage, ready to be picked up by sheep and cattle. The animals can become infected as soon as October/November from the over-wintering fluke larvae (Boray, 1969).

The above situation was confirmed in the field by the present author and colleagues in the (Sydney) McMaster Laboratory, CSIRO in a three year experiment at an irrigation area using groups of uninfected sheep exposed to pastures every six weeks. After removal from the flukey pastures, egg counts were carried out and two months later the sheep were killed and the flukes counted in the livers. The experimental sheep became infected all around the year, including winter, but peak infections occurred between October and December from the over-wintering fluke larvae in the snails and metacercariae on the herbage. The second peak normally occurs between March and June from infective larvae produced by snails during the summer period. This period is normally highly suitable for the multiplication of snails. Some of this infection was caused by the surviving metacercariae attached to grass at fairly low temperatures in May and June (Boray et al., 1969).

Subsequent research carried out at the University of Melbourne in an irrigation area of Victoria confirmed the second peak infection found in NSW. This is due to intensive metacercaria production during summer and early autumn and also to the survival of metacercariae on grass in late autumn and early

2 With various changes over the years, the CSIRO facility near Armidale NSW is now known as the McMaster Laboratory (FD McMaster Laboratory, Chiswick). – Ed.
winter. This period is normally wet in Victoria, particularly in the irrigation areas. The overwintering infection was less important in Victoria, probably due to dry conditions in late summer and early autumn, preventing the infection of snails (Meek and Morris, 1981).

Similar CSIRO trials in the Central Tablelands of NSW showed that peak infections were picked up between January and June with another peak from October until January, with much lower infection in winter. The trials in NSW demonstrated the importance of the dormant, surviving fluke larvae of the snail in winter emerging as infectious larvae in spring and summer (Boray et al., 1969).

Metacercariae on herbage

The results of the above mentioned trials were confirmed by the present author in laboratory studies carried out in controlled climate chambers in the Veterinary School of Hannover, Germany. It was shown that metacercariae survive low (-10°C) and relatively high temperatures 25 to 30°C, provided that sufficient moisture (90% or more relative humidity) was present. At low temperatures –1 to 2°C the metacercariae survived longer with a high rate of viability, supported by tests in laboratory animals (Boray and Enigk, 1964).

In the irrigation areas in Australia, moisture is present throughout the year, including winter, resulting in infections all year around from surviving metacercariae. In the Tablelands, particularly in the Central and Northern Tablelands of New South Wales, winter is normally dry and metacercariae will survive on the grass only in springs and the surrounding areas. However, the very important temporary snail habitats are too dry for the metacercariae to survive. The metacercariae will survive in winter in the South West of Victoria in the coastal areas and in some parts of Tasmania due to higher rainfall and the presence of moisture on the grass. Most infections will occur through cercariae produced in summer, but the metacercariae will not survive in the dry, hot weather. However, the metacercariae will survive in the higher rainfall coastal areas during the whole year. The laboratory studies mentioned above suggest that metacercariae can be present in most of the endemic regions of Australia throughout the whole year. The continuous production of metacercariae can be expected in summer under moist conditions and in many regions metacercariae will survive during early winter on moist grass (Boray and Enigk, 1964, Boray et al., 1969).

Studies in the U.K. at the Central Veterinary Laboratory, Weybridge and in Australia at the McMaster Laboratory, CSIRO showed that the metacercariae live longer and are more viable in the winter months under moist conditions but no larval development occurs in the snails. Large numbers of metacercariae are produced from late spring until the end of autumn. Recent studies in Spain showed that the fluke eggs, the larval stages of fluke in the snails and the metacercariae survive during winter under the climatic condition in the Mediterranean areas of Spain. The climatic conditions in some districts of Australia are similar to those in Spain.

Metacercariae in hay

Although hay may be rarely produced from snail habitats in Australia, the survival of metacercariae in hay could be of some importance. The problem has been investigated in many countries in Europe, where hay is harvested during summer and early autumn for winter feed, often from temporary snail habitats. Those studies concluded that if the hay was collected in rainy periods and kept at reasonably high relative humidity, the metacercariae can survive the winter for many months (Boray and Enigk, 1966). Feeding cattle with rice straw harvested in irrigated rice fields is a very important means of maintaining the life cycle of liver fluke in some countries in South East Asia, Japan and Nepal. In Japan the cattle are normally kept in stables and fed with rice hay. The rice fields are fertilised with the manure of the cattle. Contamination of hay with metacercariae may also occur in Indonesia and under Australian conditions.

Conclusion

It can be concluded that under Australian conditions infection of stock may occur during any period of the year with some variation depending on seasonal / climatic conditions.

Effective fluke control can only be achieved by preventive strategic methods. Since weather conditions are unpredictable, no accurate forecasting systems are available. Strategic control should be organised by treatments according to the average climatic conditions of many years, produced by the Meteorological Bureau for each district. Weather charts, based on average temperatures and rainfall, including the expected snail activity and recommended treatments were produced and can be obtained for any regions or countries (Boray, 1993, 1997).

Correct farm management can reduce the exposure of sheep and cattle to infection by fencing in
permanent snail habitats or by using a pasture-rotation system (Boray, 1969).

Completion of the life cycle of *Fasciola hepatica* and potential infection of sheep and cattle depends mainly on rainfall or the presence of moisture and temperature. The moisture necessary for the reproduction of snails and the hatching of fluke eggs is usually provided by small permanent creeks, which are normally fed by springs. Those creeks running through paddocks and gullies support the amphibious intermediate host *L. tomentosa* in shallow muddy habitats preferred by the snail. Similar conditions are created by seepage from canals in the irrigation areas. In drought some of the springs dry up but some moisture may be still present to maintain the growth of grass which has the infective stage of the fluke. The sheep and cattle congregate around those gullies and graze the contaminated herbage, resulting in heavy acute infection in the animals.

The second important condition for the completion of life cycle and the survival of metacercariae is suitable temperature. In winter all stages of fluke development and reproduction of snails cease when the temperature is around 10°C or less, but the snails survive together with the dormant fluke larvae. The snails also survive in the mud during dry periods for about a year. During the winter the metacercariae may survive for some time on the herbage under moist conditions. The first invasion of herbage with the fluke cysts commences in late spring when the larval stages of fluke which are obtained from infection of snails in autumn complete their development (over-wintering infection). At the same time the snails rapidly multiply under the more suitable conditions and become infected by the fluke larvae (miracidia) which hatch out from the fluke eggs produced by the adult flukes in sheep and cattle. Within 2–3 months more fluke cysts will invade the herbage during the summer months (summer Infection) and reach high contamination by the end of summer and the beginning of autumn. Heavy infections may occur during this period but the clinical symptoms of acute and sub-acute fasciolosis are often unnoticed. The disease produces obvious symptoms in most cases when the parasites reach the chronic adult stage about 2 months later.

Due to progressing anaemia the economic loss is more pronounced, reducing the wool growth and bodyweight in sheep, particularly in younger animals. The clinical symptoms of the acute disease will not be obvious for 2-3 months in the spring and early summer period unless the pastures are heavily contaminated and at that time increasing mortalities may occur. Chronic fasciolosis by adult flukes in the bile ducts may be present during the whole year if regular treatments are not carried out. The chronic disease is due to adult flukes, sucking blood in the bile ducts, resulting in chronic anaemia.

**Pathology of fasciolosis in sheep**

In sheep the acute disease is due to mechanical damage when a large number of immature flukes migrate through the liver tissues and destroy functional liver cells. The inflicted damage to the liver tissues also retards growth of the flukes and the tissue migration period will be extended causing severe sub-acute fasciolosis. Peracute, acute and sub-acute fasciolosis is caused by the tissue migration of immature flukes. The pathological damage produces cell destruction causing extensive haemorrhage. Deaths are normally due to profound anaemia resulting from blood loss and the failure of liver function. However, the role of the excretion of proline and subsequent tissue changes should also be considered (Symons & Boray, 1968, Boray, 1985). Outbreaks may occur with considerable losses when seasonal and climatic conditions result in a large intake of metacercariae during a relatively short period.

Much work on the pathology of fasciolosis was carried out in the McMaster Laboratory, CSIRO (Boray, 1967, 1969). Trials were carried out with experimentally infected sheep, which involved a total of 269 animals. It was shown that in sheep with an average fluke burden of 103, clinical disease was not evident until the fluke matured and a large proportion of the sheep was suffering clinical chronic progressive anaemia causing death in some of the sheep in the higher fluke recovery groups. In two groups of sheep, which had an average of 204 flukes after experimental infection, early liver damage causing reduced liver function was demonstrated with serological tests by detecting a very high level of the enzyme glutamate dehydrogenase as early as two weeks after infection. The high enzyme levels persisted for some weeks, demonstrating the presence of liver damage, caused by acute and sub-acute fasciolosis. All of those sheep died of progressive profound anaemia 26 to 36 weeks after the inoculations.

In a group of sheep which had an average of 708 flukes in their liver after infection, the animals had acute and sub-acute clinical fasciolosis, resulting in haemorrhages and severe anaemia. All the sheep eventually died after 15 to 22 weeks infection. During decades of field work similar fluke numbers...
were often found in sheep. In one occurrence of acute and sub-acute fasciolosis in sheep an average of 1,384 flukes was present in the livers at necropsy.

In further experimental work in merino sheep aged 5 years, serious acute and sub-acute fasciolosis was observed and in a group of 58 sheep an average of 1,535 flukes was present at necropsy. All those sheep died within 7 to 10 weeks after infection suffering from severe haemorrhages and with the evidence of acute and sub-acute liver damage.

All the above sheep, including those with only around 100 flukes in the liver, had loss of appetite, reduction of weight, anaemia and thus subsequently died indicating the potential pathogenicity in the field if the animals are not treated.

In one experiment a group of sheep was infected with 500 metacercariae each and was treated with triclabendazole at 10 mg/kg ten weeks later to achieve eradication of the fluke. Ten weeks after the treatment the same procedure was repeated to inflict heavy damage in the liver and then remove the fluke. In another group a similar procedure was carried out, but each sheep was infected with 100 metacercariae only. The sheep showed evidence of successful treatment and ten weeks after the second inoculation and treatment all the sheep were inoculated with 500 metacercariae each. One group of sheep remained uninfected and untreated as controls. A high level of liver damage was indicated by the increased GLDH level in serum. Similar numbers of flukes were present at necropsy 14 weeks after the challenge infection in all the sheep, including the controls. This experiment showed that a previous infection did not generate an immune reaction against the second infection and the serum enzyme test was a useful tool for diagnosing acute fasciolosis in sheep.

In all the above experiments there was always sufficient liver damage by the flukes to explain deaths. However, in the majority of cases, secondary pathological lesions, such as peritonitis, pleuritis and traumatic damage in the lungs and pancreas, contributed to the condition. The primary damage due to the migrating flukes was detected with a single bromsulfalein clearance test as early as three weeks after infection (Symons and Boray, 1968), thus demonstrating the occurrence of liver function failure caused by immature flukes.

Strategic control for sheep

In an endemic area a curative drench has to be given in April/May, when a high level of infection is anticipated. For this treatment a product should be used which is highly effective against both early immature and adult fluke. The best treatment for this period is an oral dose of triclabendazole or its combination products, Fasinex100®, Fasimec® Sheep, Flukare®, Flukamec® etc. A highly effective formulation of triclabendazole is available as FlukazoleS®, which has an improved efficacy by the addition of oxendazole. The increased efficiency is achieved by a synergistic effect of the two ingredients and it is effective against flukes moderately resistant to triclabendazole.

The second essential treatment (preventive treatment) is very important at the end of the winter or early spring (August/September) to eliminate the flukes surviving in the sheep. Infection may be obtained by ingesting metacercariae, which may have survived on the herbage if a wet period occurs during early winter. This treatment will reduce the contamination of the pasture before the active period for the snails and the fluke commences with increasing temperatures. At that time most of the flukes would have reached an advanced immature or adult stage when another product which is effective against those stages could be used with good results. Many products are available for that purpose, but another synergistic combination product such as Closicomb® or Rota Fluke® will be the most effective for this purpose, which is highly effective against flukes resistant to closantel on many properties.

The above products include chemicals which belong to groups different from triclabendazole. This treatment would achieve an effect of drug rotation, reducing the chances of the development of resistance to triclabendazole.

In endemic areas with high rainfall in spring an additional treatment in January/February is recommended with drugs highly effective against immature fluke as mentioned above. At that period a high proportion of the flukes in the liver would be immature. The fluke larvae present in snails will stop development during winter, but as temperature rises will continue development and metacercariae will be available on the herbage (over-wintering infection). New infections may occur as the temperature rises and the snail population

Pathology of fasciolosis in cattle

It has been generally recognised that cattle are more resistant to fasciolosis than sheep (Boray, 1967, 1969, Ross, 1967). More intensive tissue reaction occurs in cattle than in sheep and in the bovine hosts a considerable age resistance is present. It has been concluded that the resistance observed in cattle is due to the combination of an early and a late tissue reaction forming a mechanical barrier against re-infection. The normally observed preferential migration of young flukes into the ventral lobe produces an effective mechanical resistance and the subsequent hypertrophy of the right lobe facilitates the survival of the host by leaving sufficient undamaged liver tissue. The dystrophic calcification of the bile ducts and the fibrosis proliferating into the parenchyma in chronic cases causes the elimination of the flukes. Calcification is not present in sheep. Relatively few results of experimental infections are available. Some results of experimental infections carried out in McMaster Laboratory (Boray, 1969) may give reasonable information on the clinical pathology expected to occur in the field.

Severe anaemia was diagnosed in a group of calves aged 6 to 8 months after experimental infections with 1,000 metacercariae each. One calf died but three calves recovered spontaneously.

A group of calves, aged 4 months, which had a mean number of 1,358 flukes in the liver, showed profound anaemia and high egg counts when the flukes reached maturity. In another group of 6 calves aged 6 to 8 months one calf died, two showed severe anaemia and two of the calves showed no clinical symptoms. They had a mean number of 1,381 flukes in the liver. When a group of calves aged 17 months was infected with the same number of metacercariae only a mean number of 620 flukes were recovered from the liver and the calves survived. In another experiment, cattle aged 6 to 8 months or 2 years were infected with 10,000 metacercariae. All the younger animals showed profound anaemia and all died of sub-acute or chronic fasciolosis. A mean number of 4,671 flukes were recovered at necropsy. The two year old cattle survived and a mean number of 512 flukes was recovered from the livers. It was also shown that calves in good condition showed more resistance than poorer ones. Some breeds of cattle were more or less resilient to fluke. In a comparative experiment, Jersey calves aged 4 months showed more serious clinical symptoms compared to Herefords of the same age after experimental infections resulting in a similar number of flukes recovered at necropsy.

It can be concluded that acute and sub-acute fasciolosis occurs mainly in younger animals with severe anaemia and death occurring on heavily contaminated pastures. It would happen more often when susceptible sheep are grazed together with calves, because sheep normally produce more eggs than cattle to contaminate the pastures. However, there is considerable evidence that even a low infection in young cattle may result in reduced growth rate, reduced pregnancy rate and delayed conception of heifers. In adult cows milk production is reduced due to sub-clinical infections with *F. hepatica* (Dargie, 1986).

**Strategic control in cattle**

Strategic liver fluke control is essential to maintain productivity of cattle even if no visual signs of clinical fasciolosis are present but positive egg counts, serological tests or ELISA tests using milk samples will confirm the presence of flukes.

The most important treatment should be carried out in April/May, when the highest level of infective metacercariae is present on herbage. At that time an anthelmintic should be used, such as triclabendazole, which is highly effective against early immature and adult flukes. The most effective product for that purpose is Flukazol-C®, which is a combination drench with synergistic action, containing triclabendazole and oxfendazole. Other products applied orally, which contain triclabendazole, may also be used. At that time none of the other products are useful in a strategic programme, because they are only effective against adult fluke. In dairies, triclabendazole preparations can be used in young heifers and in dry cows. Those products can be used in pregnant cows up to 21 days before calving. In lactating cows an ivermectin/clorsulon product can be used if it has clearance for that purpose.

The second important treatment (*preventive treatment*) is recommended to be carried out in August/September to eliminate the flukes surviving in the cattle after the Summer/Autumn period. This time most of the fluke have reached adult stage, and combination treatments such as Virbamec Plus®, Ivermect Plus® or other products effective against adult flukes can be used. Another triclabendazole treatment and particularly a Pour-On application of the drug should be avoided. From pour-on formulations delayed absorption occurs and may contribute to the development of drug resistance. The use of an alternative drug would achieve chemical rotation and reduce the chances for the development of resistance to triclabendazole.
In endemic properties with a history of heavy infections, a third treatment may be necessary in January/February. It is particularly important when spring and early summer rain would stimulate the reproduction of snails or dry periods when the animals congregate in moist pastures. This treatment is highly recommended for young cattle, which are more susceptible to infection and likely to develop clinical fasciolosis. During this period a high contamination of the herbage is expected through the maturation of “overwintering” larval stages of the parasite, when the temperature increases. An increased number of cercariae will also complete their development in the snails, which were infected in early summer. This treatment in January/February should be carried out with an oral drench preparation of triclabendazole, which is highly effective against immature flukes. Higher efficacy can be achieved if a triclabendazole/oxfendazole product (FlukazoleC®) is used with synergistic action, even against flukes moderately resistant to triclabendazole.

Dairy heifers can be treated with triclabendazole products until 21 days before their first calving. Triclabendazole resistance in sheep and cattle is present in the Goulburn Valley irrigation area around Echuca, Pyramid Hill and Shepparton. In those areas an alternative product should be used such as an injectable application of the combination products containing ivermectin and clorsulon, which is suitable for both dry and lactating cows in dairies.

It is important that in mixed grazing properties sheep and cattle should be treated at approximately the same time.

Recently two pour-on products were released to the market and the potential problems of the treatment with those products will be discussed below.

**ORAL APPLICATION OF TRICLABENDAZOLE COMPARED TO POUR-ON FOR THE TREATMENT OF FASCIOLOSIS IN CATTLE**

Triclabendazole showed high efficacy against both early immature and adult *Fasciola hepatica* in sheep (Boray et al., 1983) and in cattle (Boray, 1982). The drug is a benzimidazole derivative, but the presence of chloride atoms and a thiomethyl group and the absence of a carbamate moiety clearly distinguishes it from all other benzimidazole compounds. Its spectrum of activity is unusual.

Triclabendazole is very specific for *F. hepatica*, *F. gigantica* and *Fascioloides magna*. It lacks activity against nematodes and cestodes and other trematodes as well.

Triclabendazole is metabolised by the liver into two active forms, triclabendazole sulphone and triclabendazole sulphoxide. Both of the metabolites are active against *Fasciola* sp. It is clear that the rate at which these metabolites are produced and in what concentration will determine their efficacy against liver fluke. To achieve high efficacy against early immature liver fluke a high concentration of those metabolites are required to act against immature fluke, which are migrating in liver tissues. The adult flukes in the bile ducts are killed by those metabolites as they are excreted into the bile.

Triclabendazole given orally as a drench is absorbed from the gastrointestinal tract and quickly transported to the liver via the portal blood flow, which drains directly into the liver, achieving a high concentration of the drug, which will be quickly metabolised. Triclabendazole given either parenterally or as a pour-on will travel through the entire vascular system before it can be metabolised in the liver. The delayed absorption will produce a dilution effect and will reduce the concentrations of active triclabendazole metabolites in the liver, resulting in lower efficacy for early immature flukes aged 2 to 4 weeks. It is reasonable to say that oral dosing of triclabendazole will produce a greater concentration of the metabolites in a shorter time because the drug has direct access to the liver from the gastrointestinal tract via the portal system.

The mode of action of triclabendazole was reviewed by Fairweather & Boray (1999). Triclabendazole has a multiple action against the flukes. It seems to affect the energy-producing pathways resulting in a decrease of motility. Triclabendazole also damages the reproductive system of *F. hepatica* reducing egg production and growth of the fluke. The most significant effect of the drug is the inhibition of protein synthesis, which in turn, produces morphological damage to the integument of flukes. Most of the experimental data conforms to a microtubule-disrupting action and disruption of protein synthesis. Additional studies showed that triclabendazole is also capable of uncoupling oxidative phosphorylation and this action was greater by the sulphoxide and sulphone metabolites than that of the parent compound.

During the development of triclabendazole in the second half of the 1970s, the sheep and cattle experiments were carried out in the CIBA-GEIGY Research Centre in Australia, supervised by the
present author, who was then the Director of Research and Development in the company. It was shown that at comparative dose rates the oral formulations were superior to the injectable or pour-on formulations.

The pour-on formulation produced by CIBA-GEIGY in Basel used an excellent solvent, resulting in very good absorption from the surface of the skin. However, even at drastically increased dose rates of up to 30 mg/kg, high efficacy was only achieved against adult flukes. Experience from trials with other pour-on products, which were carried out at the Elizabeth Macarthur Agricultural Institute, NSW Agriculture in the late 1980s has shown that the age and breed of cattle and the season when the treatments were carried out greatly influenced the efficacy of a pour-on formulation. The absorption of the drug may be impaired by the dense hair growth during winter, particularly on beef cattle.

When the choice of drug for the treatment of cattle is triclabendazole, it can be concluded that the best results will be achieved by using the products or combination products of triclabendazole, which are formulated for oral application.

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LIVER FLUKE IN THE HUNTER

The literature (eg "Seddon") is a bit vague on whether or not liver fluke occurs in the Hunter
This finding is perhaps not overly surprising, as this locality is not all that far from the Northern Tablelands, one of the well-known 'flukey' areas of NSW. Whether fluke occurs in other parts of the Hunter RLPB district - and whether it is significant or not - is unclear. (Lab Refs: MN05/6640/RLR, MN05/0794/RLR, MN05/0224/ADR)

Reference


RIVERINA SHEEP WORMS - INCLUDING ML RESISTANCE

Dr Dan Salmon

Dan Salmon is the District veterinarian for the Riverina Rural Lands Protection Board. The following is from the Riverina RLPB Animal Health Newsletter Vol XIV Number 4 Spring 2005, and is reprinted with permission. – Ed.

It has been one of the worst years for sheep worms that we have seen this millennium. In fact it is probably ten or fifteen years since they have been as bad.

Coming at a time when 30% of the flocks that we (Suddes and Salmon) looked at had worms that were resistant to the macrocyclic lactone group of drenches (the latest, best and most expensive group) this is a bit of a worry. While most of the damage has been done by now it is still important to control worms going into the summer. The reason that we push summer drenching is the fact that most of the eggs that worms lay will die out through the summer. On the other hand they almost all survive for as long as the weather is cool, and there can be billions of them per hectare.

So when it is cool an effective drench will kill worms but they will be replaced from the pasture in a few weeks. On the other hand an effective summer drenching program will reduce the total number of worms available to a flock, and, more importantly, the next lamb drop.

It may seem a little strange to be drenching your ewes in November to stop lambs that are not yet born from scouring in August next year, but there you have it. If it were easy then you wouldn’t need our advice!

The other thing to remember about worms besides hitting them while they are most vulnerable is that they are as variable as the climate. That is probably because the developing worms spend so much time out in the environment rather than safely tucked away in a nice warm, moist gut. So it is important to keep an eye on what the worms are doing all the time. The simplest way to do this is with egg counts.

We recommend that every sheep producer check the egg counts of their sheep several times a year:

- When the feed hays off in late (usually) spring.
- Late summer
- Lambs at weaning

Last summer there were practically no worms, by mid winter they were rife and those who did not monitor the worms in their sheep either wasted time and money drenching unnecessarily or lost production due to worms and sometimes both.

As well as keeping an eye on worm numbers, an egg count 10 days after a drench can tell how that particular drench is working, and that is becoming a very important bit of information to have.

NEMATODIRUS - A CONVERSATION

Nematodirus ('Thin-necked intestinal worm') is usually not a big problem in sheep but under certain conditions it can be! This parasite’s little speciality is its hardy egg. It can survive a long time on pasture under tough, droughty conditions and then - with a break in the season (good rain) - young sheep in particular can pick up sizeable burdens of.
Nematodirus in a short time. The result may be scours and ill-thrift, sometimes with low or even zero Nematodirus faecal egg counts.

Dr John Evers - District Vet at the RLPB at Young - tells me they have had Nematodirus problems two years running in autumn drop lambs in his district. In one case lambs were drenched with a known effective drench at marking, and three weeks later had a clinical problem with Nematodirus.

The reasons for this may be the weather pattern in Young and other districts for the last two years: a very dry autumn, and a season break occurring a month or so later (~ May/June) than usual. Nutritionally stressed late-pregnant and lactating ewes perhaps were passing more Nematodirus (and other worm) eggs in the faeces than usual, and this contributed to lambing paddocks being more heavily contaminated than in normal years. Young lambs, with minimal ability to handle worms, picked up significant burdens in a short time.

You might wonder about management factors, but John says that set-stocked as well as rotationally grazed farms have been affected.

The solution? Regular WormTesting (worm egg count monitoring) is one of the pillars of good worm control, but in unusual seasons, this may sometimes pick up Nematodirus problems after 'the horse has bolted'. This is one obvious situation where local, expert knowledge (vets like John Evers for example) is invaluable.

Other comments on Nematodirus:

Dr Justin Bailey (Veterinarian and PhD student at the University of New England).

Hi Steve – ‘Just a brief comment with regards to Nematodirus. Results from worm monitoring at Veterinary Health Research, Armidale certainly bear out the value of using levamisole against Nematodirus - in fact it is the only drench consistently found to be fully effective against this parasite. (Another vet replied with information on the value of a particular product against Nematodirus but, as this was not a registered claim, it cannot be reproduced here. –Ed).

However, a case of scours and ill-thrift in a weaner mob in the New England last year provides a cautionary tale and underlines the potential significance of Nematodirus. The weaners in question displayed scours and ill-thrift in >20% of the mob with a mean FEC of not much more than

100epg for Nematodirus and minimal other roundworm infection. Treatment with levamisole did not alleviate the clinical signs, although a further monitor indicated that the treatment had been fully effective. An autopsy on one of the more severely affected animals showed little in the way of gross pathology. However, subsequent histopathology clearly demonstrated the effects of the prior Nematodirus infection on the gut lining. This resulted in continued scours and ill-thrift for a considerable period of time after the successful resolution of the infection. The cost in terms of lost animal production would have been significant. (UNE Armidale 22 Aug 05).

Dr Dan Salmon (District Veterinarian, Riverina RLPB, NSW)

(Regarding the efficacy of various drenches…) That pretty well agrees with the results Harry Suddes and I got in our survey last year.

We found that

- on 14 ex 17 farms, levamisole had 100% efficacy (faecal egg count reduction) against Nematodirus, on 1 ex 17 the efficacy was 99%; and on 2 ex 17, the efficacy 89%.

- For albendazole we found 1005 efficacy on 5 ex 17 farms, 95-99% on 4 ex 17; 85-94% on 3 ex 17, and <85% on 6 ex 17 farms.

Of interest we are seeing more worms than for 15 years, mostly Ostertagia and Nematodirus, some almost pure growths of Nematodirus with significant clinical problems.

(Comment: because Nematodirus faecal egg counts (FECs) are usually low and variable, efficacy based on FEC reduction post-treatment needs to be interpreted with caution. – Ed).

Dr Brown Besier (Senior Vet Parasitologist, Albany WA):

Hello Steve - One point possibly of relevance - in WA, at least, is that we find that levamisole is still usually effective against Nematodirus. Where we see almost all Nematodirus eggs in a count, and virtually no strongyles, it is an opportunity to use a drench of otherwise little use (in situations where there is no Haemonchus).

(The same applies in NSW: few if any Nematodirus eggs are seen in a count following a levamisole
drench, whereas some Nem eggs are commonly seen post-BZ drenches.

So, this is the situation with levamisole:

- **Resistance in small brown stomach worm (Ostertagia/Teladorsagia) and black scour worm (Trichostrongylus) is very common**

- **Barber's pole worm is still susceptible to levamisole on most farms, but this is now changing.** (It would be wise to consider routinely using levamisole in combination with other drenches, eg naphthalophos).

- **Levamisole still seems to be effective against Nematodirus.** – Ed)

Dr Paul Mason (Consultant Parasitologist, Dunedin, New Zealand)

_Nematodirus_ is a common parasite of lambs in the South Island of New Zealand. The emphasis in the previous sentence is on lambs, because the involvement of ewes in the life cycle on _Nematodirus_ is minimal. [When I worked in the MAF diagnostic lab, finding _Nematodirus_ eggs in ewe faeces was a good indicator for Johne's.]

On many farms lambs can become heavily infected with _Nematodirus_ about a month prior to weaning, and many of the pathogenic effects can occur before the worms have started laying. This would suggest that these _Nematodirus_ require a period of cold during their free-living time (as occurs with _Nematodirus_ species in the UK) and that a synchronised hatch has occurred in the spring. If such an outbreak is unexpected, the cause is not detected until the lambs are passing eggs, so considerable pasture contamination with _Nematodirus_ eggs has occurred by the time of diagnosis and treatment. When this happens we know that there is the potential for the same condition to develop next season to lambs on the same pasture. So, we have _Nematodirus_ with a one year life cycle that is essentially restricted to cycling through lambs.

On farms where _Nematodirus_ is expected pre-weaning farmers routinely drench lambs 3 to 4 weeks before weaning, usually early November.

In support of this diapause is the observation that _Nematodirus_ is erratic to grow in larval culture. I achieved much better yields in culture when I incubated for 10 days, put the culture in the fridge for 14 days, then incubated for a further 10 days.

Many years ago I read somewhere in the literature that age resistance to _Nematodirus_ is a threshold effect and occurs after exposure of the lamb to a particular number of worms, which may explain why it occurs somewhat erratically through a mob of lambs. But we used to find that there was little point in running a FECRT for _Nematodirus_ after about mid-January. The first effect of age resistance was a suppression of egg laying by the _Nematodirus_ worms, so it was common at this time to cut open a lamb and find a _Nematodirus_ burden, even though there were no _Nematodirus_ eggs to be seen in the faeces. (NZ 19 Aug 05).

**LEJAMBRE’S CO-EVOLUTION THEORY**

(Well-know parasitologist Dr Leo Lejambre is a Post-retirement Fellow, formerly Senior Principal Research Scientist, with CSIRO, Armidale NSW. – Ed)

Some time ago, while chatting with Leo Lejambre about sheep and worms (what else?), he outlined his theory of the co-evolution of sheep and their worms.

This theory may not be entirely new, but here is an outline:

Sheep evolved in central Asia, as did black scour worm (Trichonstrongylus spp) and small brown stomach worm (Ostertagia (Teladorsagia) circumcincta). Sheep and these two species of nematodes co-evolved to the point that they were commensals and not hosts and parasites.

Barber's pole worm (Haemonchus species) and nodule worm (Oesophagostomum columbianum) evolved in African ruminants eg antelope.

Eventually sheep ended up in Africa, meeting up with Haemonchus and Oesophagostomum comparatively late in their evolutionary history.

*Haemonchus and Oesophagostomum are more pathogenic to sheep than Trichostrongylus and...*
Ostertagia. Consequently, when sheep are exposed to Haemonchus or Oes. columbianum, there is a large advantage to being able to resist infection - the alternative is death. In response to this strong selection for resistance to Haemonchus sheep evolved an immune response to gastrointestinal nematodes. This response also included the former commensals, Ostertagia and Trichostrongylus, which share many antigens with Haemonchus. The immune response to gastrointestinal nematodes is appropriate when infected with Haemonchus but inappropriate for infections with the commensals - Ostertagia and Trichostrongylus. That there is a strong selection for resistance can be seen in the highly resistant (to Haemonchus) Red Masai sheep. The heritability of faecal egg counts in this breed is zero, meaning that there is no genetic variability between animals in this trait. Selection has gone as far as it can and this was done naturally and not be geneticists.

More recently some research has come to light which supports the 'Lejambre theory'. For example work by Greer and others (2005; see below) suggest that many of the adverse effects of infection with the Ostertagia and Trichostrongylus in sheep are due to the immune response mounted by the host, rather than intrinsic pathogenic effects of the parasites themselves. They found that immunosuppressed sheep (by way of corticosteroid treatment) harboured large worm burdens with seemingly few ill-effects.

This raises important questions. How much of the pathology associated with worm infections is due to the

- worm species themselves evoking a stronger immune response (or being less tolerated). (Worms poorly adapted to the host)
- the host (individual sheep or strains) being more resistant to/less tolerant of particular worm species. (Host poorly adapted to the worms)

Following is the paper by Greer and others.

ESTIMATES OF COST OF IMMUNITY FROM IMMUNOSUPPRESSION STUDIES

AW Greer\textsuperscript{a}, RW McAnulty\textsuperscript{a}, M Stankiewicz\textsuperscript{a}, RS Green\textsuperscript{b}, AR Sykes\textsuperscript{a}.

\textsuperscript{a}Lincoln University, New Zealand; \textsuperscript{b}AgResearch Wallaceville Animal Research Centre, New Zealand.

Abstract from the 20th International Conference of the World Association for the Advancement of Veterinary Parasitology 2005

A conventional interpretation of the effect of gastrointestinal nematode parasitism on animal performance has been that damage caused by the parasite disrupts feeding behaviour, nutrient absorption and increases maintenance costs of repair of damaged gastrointestinal tissue with consequential repartitioning of nutrients to the latter function, causing a reduction in the efficiency of metabolisable energy utilisation.

Recently, the hypothesis that the host immune response per se may be responsible for repartitioning of nutrients and impaired performance has been advanced through several workers, though the potential magnitude of this component has not been quantified. We have conducted a series of trials with abomasal and intestinal infections in sheep in which the effects of the immunosuppressive corticosteroid methylprednisolone acetate has been used in an attempt to quantify the role of the immune system in this repartitioning.

Studies with naïve and resistant hosts have provided strong evidence that the characteristic depression of appetite in subclinical infections is associated only with the phase of acquisition of immunity and not a mature established immune response, and can be abolished by treatment with corticosteroids. More specifically, the depression of appetite appears to be associated with changes in serum L3 specific IgA, perhaps implicating immune system signalling. Evidence will be presented to suggest that response to this signalling may be dependent on dietary protein supply. Animals treated with corticosteroids during the phase of acquisition immunity do not suffer the typical reduction in efficiency of utilisation of metabolisable energy, suggesting the immunological cascade and cell proliferation operating at this time imposes a significant nutritional cost to the animal.

HAEMONCHUS AND WORMKILL SL

At the risk of stating the obvious, current conditions (Nov-05) are excellent in the New England region.
for *Haemonchus contortus*, the dreaded barber’s pole worm of sheep and goats (and even calves sometimes). *Haemonchus* could be important in DrenchPlan areas also if above average rain is received over summer.

- Barber’s pole worm (BPW) is one of the top three round worms of sheep in Australia: there other two are black scour worm and small brown stomach worm.
- The survivability of the infective larvae on pasture of these three worm species is roughly similar: the big difference is in the eggs.
- The eggs of these three worm species look alike under the microscope, but BPW eggs are sensitive to cold and desiccation. This is BPW’s Achilles heel: without adequate warmth and moisture within a week of being deposited on pasture, the eggs die. This is why rotational grazing systems work particularly well with barber’s pole worm.
- Because it needs moisture, BPW likes summer rainfall areas. However, it can be a problem in other parts of NSW in wet summers (say >50mm rain/month).
- BPW counteracts its Achilles heel by being a great egg layer. Adult BPW females in the sheep’s abomasum can produce about 10 000 eggs per day. This is about 10-20 times higher than black scour worm and brown stomach worm.
- Under good conditions, BPW numbers can build up quickly on pasture. Under very favourable conditions, BPW can kill sheep within 3-4 weeks of being given a short-acting drench and returned to heavily contaminated pasture. Regular egg count monitoring, and moves to low-worm risk pasture, are required if using short-acting drenches in a bad BPW season.
- BPW of course is a blood sucker, and easy to see (‘bleedingly obvious’) in the 4th stomach of sheep at post-mortem examination. Each worm can suck around 0.01 ml of blood a day, which doesn’t sound much for an adult sheep with say 4 litres of blood. However, a sheep with 10 000 worms (a heavy burden) could lose about 700 mls in a week, almost 20 % of its blood volume.
- Of the top three round worms of sheep, BPW is the one most able to overcome the immunity of sheep.

- Notwithstanding this, nutrition and genetics have a big impact on how well sheep deal with BPW.

- Control with drenches
  - Not surprisingly, long-acting drenches are very popular for BPW control! (Especially if they have not been crippled by resistance). These include closantel, capsules (ivermectin and BZ types), and various moxidectin products.
  - The upside of long-acting effective products is good control and peace of mind. The downside is that, generally you pay the price of increased potential selection for drench resistance, whether in BPW or other worms. HINT: if you use long-acting products, make sure you monitor worm egg counts roughly half way through the period of protection.
  - More frequent treatment, monitoring, and moves to low-worm risk paddocks, will be required if short-acting drenches are employed.
  - Two short-acting drenches that still work well on most farms against BPW are levamisole (‘clear’) drenches, and naphthalophos (Rametin®, Combat®). HOWEVER, it appears that levamisole resistance in BPW is becoming more common (it’s already common in the ‘scour’ worms), so consider using levamisole in combination with other drugs (proprietary combination products, or in combination with naphthalophos), even if levamisole itself still appears to be working well.

Much of the information above is ‘epidemiology’: the interaction between worm, host, environment and management. This is the basis of the principles behind programs such as WormKill (northern NSW), DrenchPlan (southern areas) and Far/WestWorm (western areas). Some commentators get a little confused at this point (‘WormKill is no longer relevant’), not distinguishing between the principles of WormKill (which mostly remain unchanged) and the application of WormKill (which varies as resistance evolves).

In its original application, WormKill was simplicity itself (hence the greater than 90% adoption rate in the early years). Closantel for BPW (and liver fluke) control was given in August, November and February in the early versions of WormKill (1984
until mid 1990s). With its persistent activity, closantel did a superb job of controlling BPW. And the program was cut and dried, a simple prescription. Perhaps it worked too well, as the first case of BPW resistance surfaced in the late 1980s in the Warialda district. The first sign of resistance was an erosion of the period of protection.

A survey of 300 farms by NSW Agriculture and Rural Lands Protection Boards in the late 1990s showed that around 70% of farms in the New England had resistance to closantel. This drench still works on a small percentage of farms but, as few farmers test for drench resistance, most don’t really know which drenches, including closantel, are still effective.

With the benefit of hindsight, the early versions of WormKill (2-3 closantel treatments a year) were probably overkill in some areas (eg north western slopes) and seasons (drier summers). Unfortunately it seems that superb worm control generally means greater potential selection for drench resistance.

A beauty of closantel is its narrow spectrum: it’s only active against susceptible BPW, and liver fluke, so there is no selection for resistance in other worms. The macrocyclic lactone drenches (“MLs”, “mectins”) have largely replaced closantel for BPW control. But they are broad-spectrum drenches. This is good and bad. They control worms other than BPW, but they also select for resistance in these worms.

Life wasn’t meant to be easy.

NEW ESIs FOR SHEEP AND CATTLE PRODUCTS


CALF SCOURS - MLA PUBLICATIONS

Information from Dr Joan Lloyd of MLA:


These new publications are currently featured on the MLA website. There are two new Tips & Tools – one on preventing calf scours and one on treating calf scours. Hard copies are also available from MLA publications at publications@mla.com.au.

In addition to these two new Tips & Tools we have also prepared a technical review on calf scours for veterinarians. Copies of these will be sent to all Cattle Vets members in the December mailing. This document will not be available on the MLA website.

Some feedback from a coastal veterinarian (Camden area):

Dear Steve,

Many thanks for this very timely email. I have two ratepayers with problems with calf scours in beef cattle at present, and have already put these excellent publications to good use. One case where 2 x faecal samples were submitted showed a pure growth of Rotavirus with no other associated problems. Losses on this property have been 6 calves ex 60 cows calved, so it has been an expensive problem.

NEW PRIMEFACTS - NSW DPI

Recently published Primefacts


Internal parasite-related PrimeFacts

Sheep measles - another profit killer-Primefact 55
DrenchPlan - the basics-Primefact 54
DrenchPlan 2005-Primefact 14

The information contained in this publication is based on knowledge and understanding at the time of writing (December 2005). However, because of advances in knowledge, users are reminded of the need to ensure that information upon which they rely is up to date and to check currency of the information with the appropriate officer of New South Wales Department of Primary Industries or the user’s independent adviser.

Recognising that some of the information in this document is provided by third parties, the State of New South Wales, the author and the publisher take no responsibility for the accuracy, currency, reliability and correctness of any information included in the document provided by third parties.
PC SEASONS GREETINGS

Please accept with no obligation, implied or implicit our best wishes for an environmentally conscious, socially responsible, low stress, non-addictive, gender neutral, celebration of the winter solstice holiday, practiced within the most enjoyable traditions of the religious persuasion of your choice, or secular practices of your choice, with respect for the religious/ secular persuasions and/or traditions of others, or their choice not to practice religious or secular traditions at all . . .

. . . and a fiscally successful, personally fulfilling, and medically uncomplicated recognition of the onset of the generally accepted calendar year 2006, but not without due respect for the calendars of choice of other cultures whose contributions to society have helped make Australia great, (not to imply that Australia is necessarily greater than any other country (world cups withstanding) in the southern hemisphere...), and without regard to the race, creed, colour, age, physical ability, religious faith, choice of computer platform, or sexual preference of the wishee.

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[Thankyou RD © - Ed.]


Best wishes to all for Christmas and the New Year

‘…no creature was stirring, not even a mouse …’