VRC Paper – LIVER FLUKE – AN EMERGING ISSUE FOR VETERINARY RESIDUES

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INTRODUCTION – VETERINARY RESIDUES & LIVER FLUKE

Veterinary medicines of many varieties play an important role in supporting healthy livestock in the fight against disease. With our weather patterns changing due to climate change, perhaps some of the most important medicines are those used to treat parasitic diseases. Currently, alternative methods are limited and so there is increasing use and reliance on medicinal-control – anthelmintics.

It is vital to achieve the right balance between supporting the availability of critical veterinary medicines such as flukicides for a sustainably productive and welfare friendly livestock industry, while preventing unacceptable levels of residues of those medicines entering the food chain.

Fasciolosis caused by liver fluke (fasciola hepatica) is a widespread parasitic disease of ruminant livestock[1]. Liver fluke is found to be endemic in many parts of the UK, especially wetter regions such as Wales and N.W England[2]. However, the incidence of fasciolosis in cattle and sheep has been increasing over the past decade (VIDA data) and in England prevalence has been shown to have increased from an estimated 48% in 2003 to 72% in 2006/7[2]. Figure 1 below illustrates the significance of the emerging challenge with approximately 16% of all diagnosable conditions submitted to AHVLA in 2013 recorded as fasciolosis[3]:

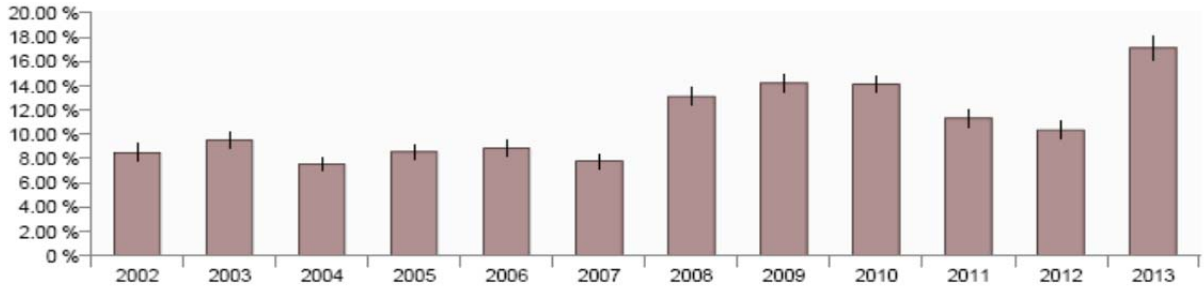

Fig.1 GB incidents of Fasciolosis in Cattle as % of diagnosable conditions

Source: AHVLA

Complex relationships exist between endemic diseases such as fasciolosis and food productivity; liver fluke can affect youngstock and adult stock in beef and dairy herds. Consequently, greenhouse gas (GHG) emissions from the cattle livestock sector are significantly impacted by fasciolosis relative to fixed outputs of kg of milk or beef. Control of fasciolosis is therefore critically important in mitigation of climate change impacts associated with the livestock industry [4].

Following the discovery in Ireland of residues in milk of certain anthelmintics active against liver fluke (flukicides) for which no milk maximum residue limit (MRL) had been established, in June 2010 the Irish Medicines Board submitted applications to the European Medicines Agency (EMA) to have MRLs established for clorsulon, closantel, nitroxynil, rafoxanide and triclabendazole. At the request of the European Commission, the applications were re-submitted under a different legal basis in August 2011. In December 2011, the EMA's Committee for Medicinal Products for Veterinary Use (CVMP) adopted opinions for provisional milk MRLs for closantel, clorsulon and triclabendazole and a final milk MRL for nitroxynil. These opinions were considered by the European Commission and subsequently milk MRLs were entered into the Annex to Commission Regulation (EU) No 37/2010. Marketing Authorisation Holders subsequently applied to vary their Summary of Product Characteristics (SPCs) for relevant products once the MRLs were published.

In March 2011 the Commission initiated a separate procedure under Article 35 of the Veterinary Medicinal Products Directive (2001/82/EC) requesting the CVMP to give its opinion as to whether measures were necessary to ensure that use of veterinary medicinal products containing flukicides for which MRLs had not been established in milk during the non-lactating period would lead to residues in milk that could be of concern to consumer safety.

The situation for dairy cattle became even more challenging in November 2012, when the European Commission banned the use of specific flukicides containing triclabendazole, rafoxanide and nitroxynil in animals producing milk for human consumption, including the dry period. However, the flukicide 'Fasinex 240', (containing triclabendazole), from Novartis Animal Health was subsequently granted a variation approval allowing it to continue to be used in cattle producing milk for human consumption. However, this product is subject to certain restrictions and it is important that these are discussed with the prescribing veterinary surgeon before use. Oxyclozanide has also recently been reauthorised as 'Zanil' by MSD animal health for lactating dairy cattle with a 72 hour milk withdrawal.

Against this backdrop of EU directed product market authorisation change and climate driven increase in liver fluke incidence, the Veterinary Residues Committee (VRC) highlighted the need for ongoing education and surveillance in this area.

LIVER FLUKE-DISEASE DYNAMICS

The distribution of liver fluke is determined primarily by climatic conditions that are favourable for the intermediate host snail (Galba) and early stages of fluke development; particularly warmer weather and more rainfall[2]. Longer grazing seasons exacerbate the problem due to increased exposure to the risk period. 2012 was one of the wettest summers on record in the UK, resulting in the emergence of fasciolosis in regions of the UK not previously recognised as endemic areas, such as has occurred in N.E England. This has created a huge threat to both sheep and cattle in the UK, which in the face of increasing anthelmintic resistance, represents a significant problem impacting on health, welfare and productivity.

Globally, Fasciolosis has a major economic impact on the livestock industry as a result of mortality, liver condemnations and lost production[2]. Carcass condemnation due to liver fluke stands at a reported 306,499 (19.81%) in 2010 which represents an estimated loss of

£1,225,996 (EBLEX). EBLEX estimates liver fluke costs the UK beef industry £8-9.5 million/year with losses of productivity amounting to as much as £25 to £30 per case. Production losses including milk yield reduction of 2kg/cow has been shown in infected herds, however reported impacts of liver fluke on reproductive performance are inconsistent in the literature, probably due to differences in infection level and health status[1]. Currently, only one licensed treatment (triclabendazole) is available in the UK against immature stages of liver fluke and increasing levels of resistance are threatening its efficacy.

The lack of sensitive and convenient diagnostic tests represents a challenge in controlling fasciolosis in large herds as well as in monitoring treatment efficacy. No commercial vaccines are currently available for the prevention of fasciolosis, hence control is based largely on anthelmintics and risk avoidance management strategies[2]. Thus, there is an urgent need for accurate and early diagnostics, strategic advice on appropriate use of diagnostic tools and improved understanding of the production impacts of endemic infection.

DIAGNOSIS

Diagnosis is largely based on coprology and microscopic identification of parasite ova in faecal samples. Low sensitivity (30-60%) caused by intermittent shedding and a delay of 10-12 weeks post-infection limits the usefulness of this diagnostic test. Individual serology using immunological techniques detects circulating antibodies within 3-5 weeks post infection, however the limitations of blood sampling in large herds and the detection of antibodies persisting after parasite clearance affect practical application. Bulk milk ELISA is commonly used as a herd level monitoring tool, but as with serology requires careful interpretation regarding historic exposure.

More recently, the development of enzyme-linked immunosorbent assay (ELISA) test to detect parasite antigen in faecal samples (coproantigens) has offered the opportunity of an alternative diagnostic tool. Coproantigen ELISA avoids the practical limitations of blood sampling and has been demonstrated to have the ability to detect infection 5-6 weeks post infection. Concerns have been expressed over the effectiveness of the test for detecting low-intensity infections, particularly in cows where dilution of coproantigens due to faecal volume will be high. However, the test has been demonstrated to pick up low infection levels (1-2 fluke) in cattle[5]. The specificity of the test for fasciola hepatica has also been quoted as a benefit of this diagnostic test. Rumen fluke (*paramphistomum cervi*) is becoming increasingly common in the UK and demonstration of lack of cross-reactivity of rumen fluke with liver fluke coproantigen ELISA adds value to its diagnostic use[6].

TREATMENT & CONTROL

Before embarking on a liver fluke treatment regime it is important to determine whether a fluke problem actually exists on a farm. Treating unnecessarily costs money and time, and promotes resistance. Feedback on liver condemnations is available from abattoirs and routine faecal worm egg counts, (FECs) may be performed on representative groups. If this is done frequently enough to compensate for the low sensitivity of currently available

testing it is possible to build a genuine picture of the overall parasite burden on farm, not just liver fluke.

Environmental controls are based on separation of cattle from snail habitats by fencing -off or draining wetlands. However, this is often impractical or inappropriate and so therapeutic approaches are common.

To control liver fluke, there is often a need to treat strategically with a flukicide product tailored to the stage of the fluke lifecycle. The stage of the fluke lifecycle is determined by the time of year and local farm factors such as climate, ground conditions, grazing management, stocking density, etc. As a result the dosing regime must be tailored to the **individual farm.** There is no such thing as a 'routine' or 'blanket' control program. A Fluke control program should be incorporated into the individual farm's health plan.

As with all medicines, appropriate storage and use is important. For example, the Fasinex SPC reads "protect from frost"and the Combinex data sheet reads "store in a dark place below 25C" (Novartis animal health). Data sheet content is vitally important as failure to abide by these guidelines may result in reduced drug efficacy. Farm medicine storage and vehicle facilities used while medicines are in transit are often sub-optimal; the dashboard of the pick-up is not a suitable medicines cabinet.

Accurate dosing according to weight is very important as underdosing is a strong driver for resistance, whilst overdosing risks toxicity. As a rule of thumb, treatment should be according to the heaviest in the group. If wide weight variation exists splitting groups into 2, allowing for smaller and more even groups should be followed by dosing to the heaviest in each group. It is vital to ensure that all drenching equipment is clean and correctly calibrated before use and products are not mixed in the same drench.

Once fluke is confirmed on farm, the following can be used as a framework for an individual farm fluke control program:

- Treatment frequency during the grazing season will depend on environmental conditions eg wet summers provide greater habitats for the intermediate host snail and encourage proliferation of both the snail and fluke. NADIS provide regional forecast summaries which help to decide treatment protocols.

- Only a limited number of products are available and not all will kill all the different stages of the fluke life cycle eg triclabendazole has activity against the mature and immature fluke down to 2 weeks in cattle, whereas nitroxynil injection only has activity down to 6 weeks, (so fluke less than 6 weeks old will not be killed by nitroxynil). Albendazole only kills adult fluke. Variation also exists between the different methods of application eg oral preparations generally kill younger stages than pour on preparations.

- Most of the liver damage is caused by the migrating immature fluke. The inability to kill the earlier stages means that repeat treatments may be needed approximately 8-10 weeks later - those fluke in the earlier stages will then be within the susceptible age and any adult flukes developed since the last treatment can be killed before they start producing large numbers of eggs.

- Treat with the right product at the right time of year remembering that a product that kills immature stages may be needed in October, and mature stages in January. Repeat treatments effective against mature stages such as albendazole administered after housing may allow reduced reliance on vulnerable products such as triclabendazole, as immature stages mature and become susceptible to a wider range of flukicides.

- Treatment for an acute outbreak of disease may include the use of a product containing triclabendazole as this is expected to kill all stages of the parasite. However, increasing concerns over resistance, are prompting more prudent use and alternative products e.g. closantel, which will remove any late immature or adult flukes may be more appropriate in cattle.

- Resistance, (especially to triclabendazole), is increasing so any perceived treatment failures should be thoroughly investigated using faecal egg reduction assays.

- Perform regular FECs – however egg shedding is intermittent, and none are produced until adult fluke are present 12 weeks after infection, so sensitivity can be disappointing.

- Investigate all case of illthrift – remember plenty of other causes exist e.g. dental disease, lameness, trace element deficiency, chronic conditions such as Johne's disease and scrapie etc.

- Investigate sudden deaths – clostridial disease commonly causes sudden deaths secondary to liver tissue damage caused by an underlying fluke problem.

- Quarantine bought-in stock and administer a flukicide to avoid introducing fluke in animals carrying the parasite. As levels of resistance to flukicides rise, it may become prudent to dose using 2 different fluke medicines serially at quarantine

- No flukicide currently available offers any persistent action – so reinfection can occur immediately after treatment.

RESIDUES SURVEILLANCE RESULTS

There has been a small but steady stream of non-compliant results for flukicides in recent years under the UK's statutory surveillance programme, although significantly more non-compliant results have been recorded under the separate meat inspection schemes operated in Northern Ireland in the last two years. This emphasises the need for accurate dosing according to weight as discussed above.

VETERINARY RESIDUES – CONCLUSIONS

Flukicides are emerging as an increasingly important class of veterinary medicines as climate change potentially contributes to the wider distribution of fasciolosis as a threat to cattle and sheep farming. A lack of robust alternatives is leading to a reliance on chemical control and consequently significantly increased use of flukicides in livestock farming. Appropriate use of products and respect for withdrawal periods is important to avoid inappropriate veterinary residues in food and there is a need for continued research into effective alternative methods of control.

In checking the correct use of products residues surveillance under the National Surveillance Scheme must be appropriately targeted, and have the flexibility to respond to extreme weather conditions in particular areas. It is vital that the cattle and sheep sectors are vigilant to the threat of anthelmintic resistance, and that there are mechanisms in place to share intelligence with the Government and other key stakeholders.

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