Resistance to fasciolicides

Resistance in the UK

At the time of writing, the only flukicide for which there is confirmed resistance in the UK is triclabendazole (TCBZ). TCBZ is the most widely used flukicide because of its activity against immature fluke. Unfortunately, this has led to the development of resistance in several countries and reports of suspected resistance in the UK continue to increase. The prevalence of TCBZ resistance across the UK is very difficult to quantify because there is no routine surveillance. However, studies using a combination of faecal egg count reduction test (FECRT) and/or Coproantigen Reduction Test (CRT), have confirmed the presence of TCBZ resistant fluke populations in SW Scotland, NW England, N Ireland and other locations. ***It is very important to confirm resistance and not just assume there is resistance without testing***. Anecdotal evidence suggests that many farmers have switched away from TCBZ to other, possibly less appropriate flukicides without any evidence that resistance is present. (see McMahon, et al., 2016).

Resistance to TCBZ in liver fluke appears to develop more rapidly than resistance in roundworms. This is most likely associated with the intermediate host, the mud snail, which effectively 'clones' resistant populations and genotypes. While we do not have reports of resistance to any other flukicides in the UK, there have been reports of albendazole resistant liver fluke in sheep in Spain and closantel resistance in cattle in Sweden. This means we must be careful to preserve the efficacy of the few flukicides we have at our disposal, particularly as there are no new flukicides on the horizon for the UK market.

Flukicide resistance – how and when to test?

Faecal Egg Count Reduction Test (FECRT)

Flukicide resistance is difficult to confirm in the field because it is based on tests which can give equivocal results (particularly the FEC test). There are also other contributory factors affecting apparent flukicide efficacy, such as reinfection. However, there is a validated, statistically robust FECRT for TCBZ resistance detection in sheep, which was developed by researchers at University of Liverpool. This requires the collection and analysis of composite (pooled) FECs from a group of 12 sheep, on the day of TCBZ treatment and again 3-weeks later. This test works particularly well for TCBZ-resistance testing, because successful treatment results in no eggs reappearing for 10-12 weeks. This does not hold true for other flukicides e.g. closantel or nitroxynil, which only kill fluke that are at least 6-weeks old, so results could be confounded as remaining immatures develop into egg-laying adults in the liver over the course of the subsequent 3 weeks. For full details at Daniel, *et al.,* 2012.

Coproantigen Reduction Test (CRT)

An alternative, more rapid test of efficacy is the Coproantigen Reduction Test (CRT). This also uses groups of 10-12 sheep, but this time they are sampled individually before and after treatment. This can give a very clear indication of treatment efficacy within one week, although the standard recommended interval is 3 weeks. Although more expensive than individual or composite FECRT, CRT has become the default method for resistance testing, with/without supplementary evidence from FECs and the cELISA is a proven tool for monitoring treatment efficacy when adult liver fluke are present. However, where immature fluke are present, it is recommended that the initial cELISA is followed up with a second cELISA at least 6 weeks after treatment, to ensure that resistance expressed in the immature stages is recognised (George, *et al.,* 2017).

When to test for flukicide resistance.

As well as choosing the most appropriate test for efficacy/resistance, it is also vital to get the timing right. There is no point in testing in summer when neither FEC nor coproantigen are likely to be positive. Testing in the late autumn or early winter is much more appropriate and there must also be a sufficient number of animals in the group that are positive for fluke in order to obtain a meaningful result. Apart from the Liverpool composite FECRT for TCBZ resistance (see above), there is no real consensus on numbers, but as a guide at least 10 positive animals would be a sensible starting point.

Where there is TCBZ resistance it usually manifests firstly as a failure to kill the youngest immatures, resulting in the re-appearance of fluke eggs in the faeces earlier than would be expected if the TCBZ had been fully effective. As resistance develops, even adult fluke are able to survive treatment. Also note that while resistance to a flukicide, may be selected in one host species, (usually sheep because they are treated more often), other livestock (and humans) can become infected by ingesting the resultant metacercarial cysts.

Where resistance is suspected to a particular product, then an alternative flukicide should be considered, taking into account the variations in activity against immature fluke between products. The situation is not as clear cut as resistance in roundworms. The possibility of other reasons for flukicide failure should always be considered, particularly if animals are in poor condition or may be suffering from liver damage. There are a number of other reasons why treatment may fail to be fully effective. These include:

- Pastures with very heavy infestations can mean that farmers are caught out by the speed at which animals become re-infected following treatment. Flukicides are not persistent, even those combined with wormer components which are
- TCBZ is widely used because it kills early immature fluke and historically has been highly effective when used correctly. It does, however, have to be partly metabolised by the liver before it can work properly and although there is currently no compelling evidence one way or the other, it is suggested that if the liver is damaged through a high fluke burden or other concurrent disease, this has the potential to reduce efficacy
- Inaccurate dosing through underdosing and/or badly calibrated and maintained equipment.
- Incorrect product choice – for example, the use of an adulticide in the autumn leaving large numbers of immature flukes untouched to continue to cause disease.

See Fairweather, *et al.*, 2020 for more.

Preventing the development of resistance

Alternating the use of TCBZ, closantel or nitroxynil should be considered where flukicides are used strategically, although additional treatments may be required in years when TCBZ is not used. Opportunities to avoid the use of TCBZ should be exploited whenever alternate drugs will give satisfactory levels of control. For example, the use of closantel or nitroxynil 3 weeks post-housing; and/or treatment of chronic infections in the spring with an adulticide, such as albendazole or oxyclozanide.

Moredun Research Institute have produced an animation, 'Fight the Fluke' to simplify the messages around disease, diagnostics, treatment and control.