

Short Communication

The Significance of Triclabendazole Resistance

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Submitted: 21 July 2017

Accepted: 08 August 2017

Published: 10 August 2017

ISSN: 2378-931X

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Abstract

Triclabendazole is the best fasciolicide available with activity against very young fluke. But there are increasing numbers of reports of resistance including failure of therapy in humans. Determining the resistance status on 'fluky' farms is essential as high mortality of sheep can occur if it is not realised resistance is present. The options for control are confined to other less effective products and failure of closantel as well could lead to the closure of some sheep farms in the UK. Preventing fluke infections through pasture management is difficult or may be impossible so development of a vaccine is urgently required.

The pathology of fasciolosis is well known and occurs as two main forms, the acute infection resulting from the migration of large numbers of immature fluke through the liver and chronic infection caused by adult fluke in the bile ducts and loss of blood giving rise to sub mandibular oedema (bottle jaw) and lost production. Acute fluke, which can be fatal, is largely confined to sheep and lambs due to the smaller size of their livers compared with those of cattle. The introduction of triclabendazole revolutionised the control of fasciolosis due to its activity against fluke as young as one week of age making it the most effective fasciolicide. The result was the over reliance on one product (monotherapy) that had the almost inevitable consequence of the selection of triclabendazole resistant fluke. The first report of resistance to triclabendazole came from Australia in 1995 [1]. Other reports followed and are summarised in (Table 1). Apart from the obvious implication for animal health, triclabendazole is used in treatment of human infections with *F. hepatica* and failure of triclabendazole has been reported in infected patients in Peru [2]. The implications of triclabendazole resistance can be severe when its presence has not been recognised. In central Wales a farmer informed his veterinary surgeon that he had used triclabendazole in September and in November his sheep were sick. Treatment with triclabendazole was recommended with faecal egg counts after 3 weeks. As triclabendazole had not worked treatment with closantel was given but it was too late and 60% of the flock died [3].

For a long time sheep farmers have been advised to establish the anthelmintic resistant status of nematodes on their farms due to the widespread occurrence of anthelmintic resistant nematodes, but so far this has not been adopted widely [4]. Now a similar recommendation must be made for all farms where liver fluke infections are known to occur especially where triclabendazole is used. A recent survey in Northern Ireland fortunately suggests fluke control practices are beginning to change [5]. It is also important that the effectiveness of other

fasciolicides is established as resistance has been described to some alternative therapies (Table 2). The biggest concern is that resistance will be described to closantel, the other product used in sheep. Closantel, which is only effective against immature fluke from about six weeks of age, is more toxic and less effective than triclabendazole. Another uncoupler, nitroxylnil, is used in cattle as it can be injected whilst triclabendazole is usually given orally to sheep. However, Novobilsky et al. [6], described the failure of closantel pour-on on cattle in Sweden. If due to resistance it could be of considerable concern as no therapy would be left for immature fluke in sheep. However, some veterinary

Table 1: Reports of triclabendazole resistance in *Fasciola hepatica*.

Date	Place	Reference
1955	Australia	1
2000	Wales	17
2000	Ireland	8
2001	The Netherlands	18
2006	Spain	19
2008	Brazil	20
2013	Peru	21
2015	Australia	22
2015	Northern Ireland	23
2015	Philippines	24
2016	Sweden	25

Table 2: Resistance to fasciolicides other than triclabendazole.

Date	Country	Fasciolicide	Reference
2006	Spain	Albendazole	19
2013	Argentina	Albendazole	26
2014	Argentina	Albendazole	27
2014	Spain	Albendazole	28
2014	Spain	Clorsulon	28

surgeons in Wales have been advising farmers against the use of pour-on preparations of closantel on cattle due to their lack of full efficacy [7]. In areas where fluke are very common and there is no effective immature fasciolicides farmers may have to stop keeping sheep. Fortunately if acute fluke is not of primary concern, adult triclabendazole resistant fluke can be controlled with some other fasciolicides [8,9].

In theory farmers should be able to use combination fasciolicides which would be more effective and slow the development of resistance, but once resistance has developed to one product combinations are less effective. In practice, there are no combination products so use of alternative products at different times of year is recommended. Fluke transmission in North West Europe peaks in the autumn so this is the time when a product effective against immature fluke is required, i.e. triclabendazole. By the spring all fluke should be adult so a product effective against only adults should be used. This could prevent the release of eggs from the host to infect the new generation of snails. However, with milder winters Due to global warming, infected snails may over winter and infect the spring herbage. An increased dose albendazole appears to be the product of choice, but albendazole resistance has already been described (Table 2).

In the upland areas of the UK *Nematodirus battus* can be a serious infection in young lambs and albendazole is usually used for control as there is presently very little benzimidazole resistance in this species and this spares the use of other anthelmintics. However, if sheep are dosed with albendazole to control adult *F. hepatica* this may encourage the development of benzimidazole resistance in *N.battus*. With the apparent growing importance of paramphistomes, at least in the British Isles [10], oxclozanide could be used as it controls adult rumen fluke [11]. However this might select for resistance in the most common fluke, *Calicophora daubneyi*, leaving no product for this infection when it is required.

Diagnosis of infection usually involves the counting of fluke eggs in faeces at the time of treatment and three weeks later. This time is required to allow the breakdown of adult fluke in the liver and expulsion of all eggs. Unlike with nematodes release of fluke eggs from the liver/gall bladder into the faeces is not continuous so several animals must be tested to ensure fluke infections are not missed. In this regard use of composite sampling can reduce the costs of tests [12]. Immunological tests have been developed but have not yet been widely used for routine diagnosis [13]. However, they do have the advantage of detecting the presence of immature fluke infections. Another method of detecting resistance may be the use of FAMACHA which determines the degree of anaemia by inspecting of eye colour [14]. However, it cannot be used where there is *Haemonchus contortus* this nematode causes anaemia.

In an ideal world, farmers would prevent the introduction a triclabendazole resistant fluke through the movement of animals. But given the long pre-patent period (10-12 weeks) and thus the need to keep animals off pastures where there may be snail intermediate hosts this is unlikely to be adopted. Once triclabendazole resistant fluke are in an area they can be spread by rabbits and deer which are good final hosts. So, without a

rabbit proof fence that is too high for deer to jump over, spread of triclabendazole resistant fluke is almost inevitable. Another recommended method for control is to either fence off 'fluky fields' or wet spots in fields, e. g. areas around natural springs which are sufficiently moist to support the intermediate snail host (*Galba truncatula*, or related species). But in hill country in the UK this method of control is not practical particularly where there is common grazing land. In the UK and presumably some other countries spraying of molluscicides is prohibited due to the risk of contamination of water supplies. Drainage of upland fields is also strongly discouraged so that rainfall is slowly released from the land which ensures amore steady flow in the rivers rather than rapid run off. This is particularly important where drinking water is extracted from rivers. Wet land conservation is also encouraged to maintain biodiversity with grazing for vegetation control. This, of course, encourages infection of animals.

Even if a new fasciolicide with a different mechanism of action has already been discovered, it takes a long time to develop and is very expensive. So alternative methods of control are required and the obvious answer is development of vaccines. Efforts have been expended on proteins as potential vaccine candidates so far without a vaccine fully effective in grazing animals [15]. The development of resistance to triclabendazole has complicated the control of liver fluke [16] and the use of alternative products is not as straight forward as at first site appears. It is to be hoped that further surveys of the resistance will be undertaken and published so that the true extent of resistance on a world basis can be established.

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Cite this article

Coles GC (2017) The Significance of Triclabendazole Resistance. *J Vet Med Res* 4(7): 1098.