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REVIEW

THE PHARMACOLOGY OF FLUKICIDAL DRUGS

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INTRODUCTION

The pharmacology of drugs used for the treatment of trematodal disease of domestic animals has been afforded much less attention than the antinematodal drugs. This may be because the world-wide market for flukicidal drugs is smaller or because the traditional flukicidal drugs were introduced at a time when less emphasis was placed on full understanding of their pharmacology. The most important trematode of veterinary interest in the UK is *Fasciola hepatica* and fascioliasis in sheep is of great economic importance. Where environmental conditions are optimal its effects can be devastating. It has been estimated that during the winter of 1879–80 3 million sheep died from fascioliasis in the UK (Mitchell, 1979).

The flukicidal drugs belong to a number of diverse groups according to their structures and mode of action. They have variable activity against parasitic stages of *F. hepatica* and have marked differences in toxicity. An understanding of these characteristics is important for the effective and safe use of flukicidal drugs.

The present review concentrates on flukicidal drugs marketed for the treatment of *F. hepatica* infestations in the UK; additionally mention is made of other important flukicidal drugs used abroad and of their activity against other parasites.

STRUCTURE AND CHEMISTRY

The flukicidal drugs may be classified into five chemical groupings (Mohammed-Ali, 1985):

1. Halogenated hydrocarbons (carbon tetrachloride, hexachloroethane, tetrachlorodifluoroethane).
2. Nitrophenolic and bisphenolic compounds and aromatic amines (disophenol, nitroxynil, niclofolan, hexachlorophane, bithionol, diamphenethide).
3. Salicylanilides (oxyclozanide, brotianide, rafoxanide, closantel, bromsalans).
4. Benzimidazoles and pro-benzimidazoles (albendazole, albendazole oxide, netobimin, triclabendazole).
5. Sulphonamides (clorsulon).

The chemical structures of these drugs are given in Figs 1–5.

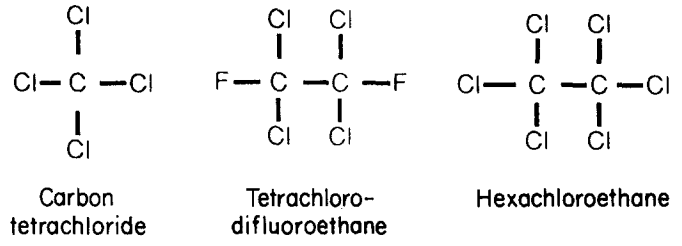

Fig. 1. Structural formulae of hologenated hydrocarbon flukicidal drugs.

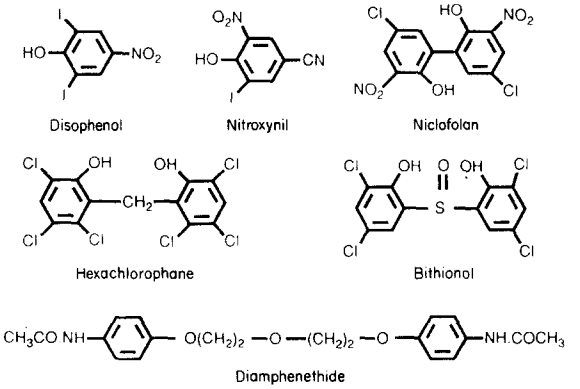

Fig. 2. Structural formulae of the nitrophenolic and bisphenolic compounds and the aromatic amines with flukicidal activity.

HALOGENATED HYDROCARBONS

The mode of action of the simple halogenated hydrocarbons against *F. hepatica* is not fully understood. Carbon tetrachloride is lethal to *F. hepatica* at much lower concentrations *in vivo* (65 μg/ml in bile) than it is *in vitro* (500 μg/ml), suggesting an indirect mode of action (Roberson, 1982). This may be by the generation of metabolites effective against the parasite (Fowler, 1971) or by modulation of the host metabolism to produce chemicals which inhibit or kill *F. hepatica* (Posthuna & Vaatstra, 1971). Both parasites and their mammalian hosts metabolize carbon tetrachloride and the metabolites are known to be toxic, causing the peroxidation of the double bonds of membrane phospholipids which may affect cellular integrity and processes that are dependent on membrane function (Fowler, 1970a, 1971; Arundel, 1985). Hexachloroethane is also known to form toxic metabolites and may act in a similar way (Fowler, 1969). It has also been suggested that methylsterols, which are intermediates in cholesterol biosynthesis, accumulate in the liver and bile of animals treated with carbon tetrachloride and intoxicate the

liver fluke (Posthuna & Vaatstra, 1971). Metabolites of carbon tetrachloride and the methylsterols both accumulate within the bile of treated animals and may therefore exert a degree of specificity for the parasite by virtue of their concentration. Histological studies indicate that the major effect on the parasite is associated with the secretory and enzymatic activity of the gut epithelium (Roberson, 1982). Carbon tetrachloride is slowly absorbed after oral administration and is metabolized to active radicals by liver microsomes in mammals (Butler, 1961; Garner & McLean, 1969). Metabolism can be accelerated by concurrent administration of microsomal enzyme inducers such as phenobarbitone. The parent molecule is excreted in bile, urine and in expired air because it is volatile, and the metabolites are principally excreted in the bile and urine.

Acute toxicity can occur following very high doses of carbon tetrachloride and is manifest by signs of central nervous system depression. More commonly, however, toxicity is delayed and is a result of centralobular necrosis and fatty changes in the liver. It is thought that damage to the mitochondrial envelope results in autolysis of the liver cells. If the animal survives, these changes are completely reversible and may be hastened by the administration of protein synthesis enhancers such as methylthiouracil (Roberson, 1982).

Toxicity may be affected in animals by alteration of the absorption, metabolism and excretion of carbon tetrachloride. Absorption can be increased by the administration of repeated small doses rather than a single therapeutic dose or by the administration in high fat diets (Roberson, 1982). The induction of liver microsomes by phenobarbitone

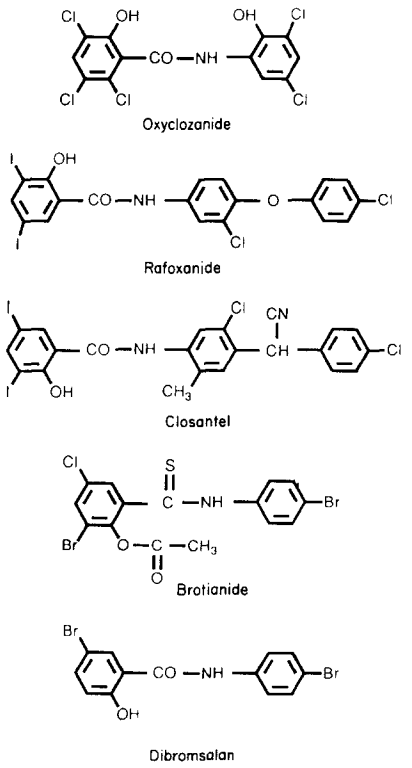

Fig. 3. Structural formulae of salicylanilide flukicidal drugs.

increases the conversion of carbon tetrachloride to toxic metabolites and thus increases its toxicity (Garner & McLean, 1969). It is also known that animals in good body condition, and presumably with healthy and active livers, are more susceptible to the toxic effects of carbon tetrachloride than those in poor condition and those with compromised hepatic metabolism which may be a consequence of their parasitic burden (Fowler, 1970b). Excretion may be affected by ambient temperature since the volatility of carbon tetrachloride and the respiratory rate of treated animals are increased at higher temperatures, thereby increasing the excretion rate of the drug and reducing the likelihood of toxicity.

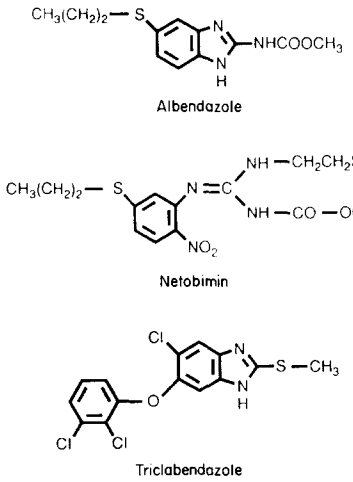

Fig. 4. Structural formulae of the benzimidazoles with flukicidal activity.

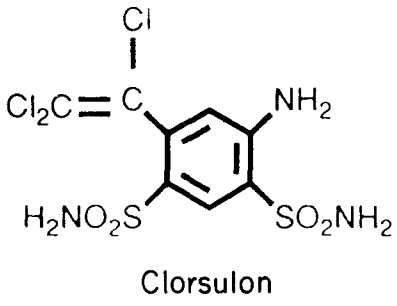

Fig. 5. Structural formula of clorsulon.

Carbon tetrachloride is much less toxic in birds than mammals. This may be because it is not metabolized to the toxic principles to the same extent in birds and it has been shown that concurrent administration of liver microsome inducers does not affect its toxicity in these species (Fowler, 1971).

Carbon tetrachloride is effective against adult liver flukes but has no activity against immature stages. It is also active against haematophagous nematodes such as *Haemonchus, Bunostomum* and *Ancylostoma.* The very narrow therapeutic index and its high potential for toxicity mean that carbon tetrachloride has been superseded by safer and more effective drugs. Hexachloroethane and tetrachlorodifluoroethane have largely similar spectra of activity and potential for toxicity.

NITROPHENOLIC AND BISPHENOLIC COMPOUNDS AND AROMATIC AMINES

Disophenol has been used as a flukicide (Boray, 1971). However, it is more commonly used for its activity against hookworm in dogs and cats (Roberson, 1982). Nitroxynil is extensively used in the UK for fluke infections in cattle and sheep. It has been shown to cause stunting of flukes which survive treatment and these parasites had reduced oogenesis and spermatogenesis. Morphologically there was vacuolation of parenchymal cells and denuding of gut columnar epithelium (Stammers, 1975). The biochemical mode of action is probably by the uncoupling of oxidative phosphorylation, since nitroxynil increased ATP-ase activity of rat-liver mitochondria and stimulated the rate of oxygen uptake by intact flukes at concentrations which correlated well with the lethal concentrations for fluke (van Miert & Groenveld, 1969; Corbett & Goose, 1971).

Plasma and tissue pharmacokinetic studies indicate that nitroxynil has a long plasma elimination half-life of approximately 8 days and that plasma concentrations remain considerably higher than tissue concentrations for at least 9 weeks after a single subcutaneous administration of 10 mg/kg (Parnell, 1970). This may be because it remains strongly bound to plasma proteins. Interestingly, low concentrations were found in liver and bile where the drug is active. Nitroxynil is used parenterally since its nitro group is reduced to an inactive metabolite by rumen microorganisms if given orally (Arundel, 1985).

Nitroxynil is well tolerated at the recommended therapeutic dose rate of 10 mg/kg. However, at higher dose rates of more than 40 mg/kg toxicity occurs and the signs of hyperpnoea and hyperthermia which have been reported suggest that the mechanism of toxicity may be uncoupling oxidative phosphorylation in the mammalian cells (Lucas, 1970; Sukhapesna, 1983). Nitroxynil also causes a transient depression in milk yield following administration in dairy cattle, may produce a local reaction following subcutaneous administration, and may stain wool or hair yellow if spilled (Lucas, 1967; Moreno, 1975; Roberson, 1982).

In critical trials in sheep nitroxynil has been shown to be highly effective against mature *F. hepatica.* However, its efficacy decreases proportionally against successively less mature stages (Stammers, 1976). In field trials it was effective against *F. hepatica* and *F. gigantica* infections in sheep (Colegrave, 1968; Roy & Reddy, 1969; Reid *et al.*, 1970). In cattle nitroxynil is almost 100% effective against mature *F. hepatica* but may be less than 50% effective against 6-week stages (Richards *et al.*, 1990) and these findings have been confirmed by studies on naturally infected cattle (Dorsman, 1969). It is also highly effective against adult *F. gigantica* in cattle (Roy & Reddy, 1969). Nitroxynil has been shown to have useful activity against the haematophagous intestinal nematodes *Haemonchus* spp., *Oesophagostomum* spp. and *Bunostomum* spp. in sheep and cattle (Guilhon *et al.*, 1970; Lucas, 1971).

The bisphenolic compounds, niclofolan, hexachlorophane, and bithionol, have similar activity against fluke stages as nitroxynil, being principally effective against adult fluke and also have a narrow therapeutic index of about 2. They are thought to act as uncouplers of electron transport-associated phosphorylation (Rew, 1978).

Diamphenethide was the first flukicidal drug introduced with activity against early parenchymal stages of *F. hepatica.* Structurally it consists of two aromatic amides linked by an ethyl ether, and it is the deacetylated amine metabolite which is thought to be active. Parent diamphenethide is inactive *in vitro*; however, the high concentrations of the metabolite formed in the liver parenchyma are extremely effective against immature fluke at this site (Harfenist, 1973). The active amine metabolite may undergo further metabolism within the parenchyma to an inactive compound which is neither toxic to the host nor the parasite and this may explain its high therapeutic index and poorer efficacy against bile duct dwelling stages of *F. hepatica* (Roberson, 1982). Diamphenethide is nontoxic at up to four times the therapeutic dose although at very high doses there may be loss of vision and wool slip. Diamphenethide owed its great popularity to the high efficacy it displayed against immature fluke stages. It is almost 100% effective against 1-, 3- and 5-week-old *F. hepatica* and is effective against the younger stages at two-thirds of the recommended dose rate of approximately 100 mg/kg (Armour & Corba, 1972; Rowlands *et al.*, 1985). The efficacy of diamphenethide decreases as the parasites mature and it is more than 80% effective against 7-week-old parasites and more than 60% effective against 10-week-old stages, although these efficacies can be improved if the dosage rate is increased (Armour & Corba, 1972).

SALICYLANILIDES

A major group of flukicidal drugs became available when the activity of oxyclozanide against *F. hepatica* was described in 1966 (Broome & Jones, 1966). These anthelmintics all have a salicylanilide structure and share common features relating to their mode of action, pharmacokinetics and toxicity. Those currently marketed in the UK include oxyclozanide, brotianide (in combination with a benzimidazole), rafoxanide, and closantel. The bromsalans are marketed elsewhere (Fascol^{R}) and a closely related drug, clioxanide, has also been used against *F. hepatica.*

In vitro the salicylanilides are known to uncouple oxidative phosphorylation in *F. hepatica* (Corbett & Goose, 1971; Cornish & Bryant, 1976; van den Bossche *et al.*, 1979; Kane *et al.*, 1980) and have been shown to inhibit succinate dehydrogenase activity (Duwel & Metzger, 1973; Metzger & Duwel, 1973) and fumarate reductase activity (Coles & East, 1974). However, in *F. hepatica* obtained from rafoxanide-treated sheep, Prichard (1978) demonstrated a change in the redox balance within the organism. Concentrations of oxaloacetate increased and malate decreased and the ratio of NAD+ to NADH changed in favour of NAD+, indicating a more oxidized state and thereby confirming that uncoupling of oxidative phosphorylation is the principal mode of action of rafoxanide. The other salicylanilides are thought to act in the same way (Rew, 1978).

The pharmacokinetics of three important salicylanilides, oxyclozanide, rafoxanide and closantel, have been examined in sheep (Fig. 6) and these drugs were found to be highly protein bound (more than 99%) and to have long elimination half-lives of 6.4, 16.6 and 14.5 days respectively (Mohammed-Ali & Bogan, 1987). The persistence of rafoxanide in

the plasma could have implications in the interpretation of efficacy studies of this drug on immature stages of *F. hepatica*. In many such studies animals are treated 4, 6 or 8 weeks after infection with metacercaria but not killed until 12 weeks to facilitate counting of the surviving parasites which are at this stage large and easily identifiable. Part of the putative efficacy of rafoxanide against immature flukes has been attributed to the persisting plasma concentrations affecting the flukes as they mature (Mohammed-Ali & Bogan, 1987). In a more critical study in which infected sheep were killed shortly after treatment or at 12 weeks after infection, closantel was shown to be effective against the immature stages at the time of treatment (Maes *et al.*, 1988).

It has been suggested that the long terminal elimination half-life of some of the salicylanilides may reflect turnover of plasma albumin to which they are bound

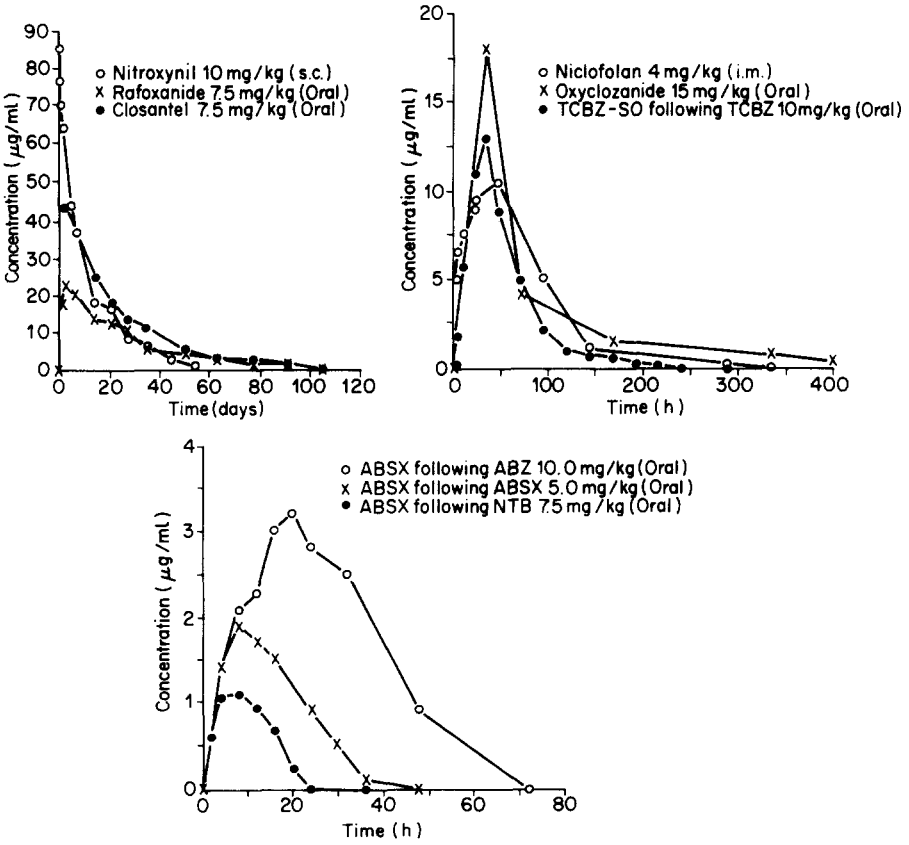

Fig. 6. Plasma concentration versus time graphs for flukicidal drugs in sheep. The dose rates of closantel, ABZ, ABSX and NTB are not those used for flukicidal activity since kinetics at flukicidal dose rates have not been reported. The large differences in the area under the curves of ABSX following ABZ, ABSX and NTB are a result of the different dose rates used. Abbreviations: TCBZ, triclabendazole; TCBZ-SO, triclabendazole sulphoxide; ABZ, albendazole; ABSX, albendazole sulphoxide; NTB, netobimin. Data derived from: Parnell, 1970 (nitroxynil); Mohammed-Ali & Bogan, 1987 (rafoxanide, closantel, oxyclozanide); Ali *et al.*, 1990 (niclofolan); Mohammed-Ali *et al.*, 1987 (TCBZ); Marriner & Bogan, 1980 (ABZ); McKellar, unpublished results (ABSX); McKellar *et al.*, 1990 (NTB).

(Mohammed-Ali, 1985) since the plasma albumin turnover rate is about 16.6 days (Holmes *et al.*, 1968). This may also be the route by which the parasites are exposed to the drug since concentrations of rafoxanide and closantel are markedly lower in bile than in plasma (Mohammed-Ali & Bogan, 1987) and adult liver flukes, against which the salicylanilides are particularly effective, are known to feed mainly on blood (Jennings *et al.*, 1956; Pearson, 1963; Rowlands, 1969). It has also been suggested that the poor activity of oxyclozanide against immature *F. hepatica* may be due to its high protein binding in blood which bathes the immature flukes in the liver parenchyma at a stage at which they are thought to feed on liver cells rather than blood (Broome & Jones, 1966). The very high degree of plasma protein binding of salicylanilides may explain the observation that in well bled out carcasses relatively low tissue residues are found and standard withdrawal periods are generally shorter than might be predicted from their plasma pharmacokinetics (Mohammed-Ali, 1985; Michiels *et al.*, 1988). It may be important to consider the residues in circulation when blood products are being used for human consumption.

The salicylanilides are not thought to be extensively metabolized, although a glucuronide metabolite of oxyclozanide has been identified (Broome & Jones, 1966). Although this metabolite concentrates somewhat in the bile it is unlikely to be anthelmintically active.

Salicylanilide drugs have approximate therapeutic indices of between 4 and 6 and the molecular mechanism of toxicity is likely to be by uncoupling of phosphorylation. Specific signs have, however, been reported for rafoxanide which include blindness and mydriasis in sheep (Mrozik *et al.*, 1969; Guilhon *et al.*, 1971) and calves (Schroder, 1982), and for oxyclozanide which causes softening of the faeces, increased frequency of defaecation, slight depression and inappetence (Boray *et al.*, 1967; Boray & Happich, 1968). Toxicity to rafoxanide is apparently more severe in sheep infected with liver fluke than in uninfected animals (Mrozik *et al.*, 1969).

All the salicylanilides show increasing activity against *F. hepatica* with increasing age of the parasitic infection (Armour, 1983) and have variable activity against many haematophagous nematodes (Egerton *et al.*, 1970; van den Bossche *et al.*, 1979; Guerrero *et al.*, 1982). Some also show activity against arthropods (van den Bossche *et al.*, 1979; Chaia *et al.*, 1981), and closantel has activity against the larval stages of *Taenia pisiformis* in rabbits (Chevis *et al.*, 1980). The stages of *F. hepatica* and the other parasites against which the salicylanilides are used in the UK are given in Table I. The good efficacy of a number of salicylanilides against *Haemonchus contortus* has made them increasingly important in areas of the world where this parasite has become resistant to other anthelmintic groups (Hall *et al.*, 1980) and this may have implications in the UK where resistant *H. contortus* have been reported recently (Taylor & Hunt, 1989). The persistence of salicylanilide in plasma may confer a prophylactic effect against *H. contortus* and permit an interdosing interval considerably longer than the prepatent period of the parasite.

BENZIMIDAZOLES AND PROBENZIMIDAZOLES

A number of benzimidazole anthelmintics have shown significant activity against *F. hepatica.* These include albendazole along with its pro-drug netobimin and its metabolite albendazole sulphoxide, luxabendazole which is not yet marketed in the UK and tri-

Table I
Flukicidal anthelmintics marketed in the UK

Drug (trade name)	*Dose rate (mg)*		*Activity against F. hepatica*			*Other parasiticidal activity*	*Meat withdrawal time*		*Milk withdrawal*
	Sheep	*Cattle*	*1–4 wk*	*5–8 wk*	*Adults*		*Sheep*	*Cattle*	*Cattle*
Nitroxynil (Trodax)	10 s.c.	10 s.c.	−	±	+	1	30	30	CI
Diamphenethide (Coriban)	105	NA	+	+	±	−	7	NA	NA
Oxyclozanide (Zanil)	15	10	−	± (3×sheep)	+	3	14	14	NIL
Brotianide (Vermadax+Thiophanate) (Flukombin+Thiophanate)	5.6	NA	−	±	+	5	21	NA	NA
Rafoxanide (Flukanide)	7.5	7.5(3.0 s.c.)	−	±	+	1,4	28	28 oral 21 s.c.	CI
Closantel (Flukiver)	10	NA	−	±	+	1,4	28	NA	NA
Albendazole (Valbazen)	7.5	10	−	−	+	1,2,3	10	14	72 h
Albendazole oxide (Bental)	7.5	NA	−	−	+	1,2,3	10	NA	NA
Netobimin (Hapadex)	20	20	−	−	+	1,2,3	5	10	48 h
Triclabendazole (Fasinex)	10	12	+	+	+	−	28	28	CI*
Clorsulon (Ivomec-F+ivermectin)	NA	2 s.c.	−	±	+	5	NA	28	CI†*

NA, not available; s.c., subcutaneous (otherwise oral); +, > 90%; ±, 50–90%; −, < 50%; CI, contraindicated; *, do not administer to dairy cows within 7 days of calving; †, do not administer to dairy cows within 28 days of calving; 1, haematophagous nematodes; 2, non-haematophagous nematodes; 3, tapeworms; 4, *Oestrus ovis*; 5, combination product.

Modified from Bogan & Armour, 1987.

clabendazole which has revolutionized the treatment of fascioliasis because of its activity against all stages of the parasite. A number of other benzimidazoles have shown some activity against *F. hepatica* but have not proven clinically useful under field conditions.

The mechanisms of flukicidal activity of benzimidazoles are not clear. Albendazole and its sulphoxide have been shown to bind to extracts of nematode tubulin, suggesting that this may be related to their mode of action. However, under the same conditions triclabendazole was without effect (Fetterer, 1986). Purified microtubular protein from adult liver fluke has been shown to bind triclabendazole and its lack of activity in crude cell free extracts may be due to non-specific binding to other proteins reducing its availability to microtubules (Bennett & Kohler, 1987). Although microtubular binding suggested a possible mode of action of triclabendazole the authors pointed out that if this was the case it was strange that the drug had such a high specificity for fluke and was ineffective against nematodes susceptible to other benzimidazoles. Bennett & Kohler (1987) also demonstrated that while triclabendazole (25 μM) immobilized adult *F. hepatica* these parasites still produced volatile fatty acids, indicating that it did not inhibit the flukes' energy generating pathway. It may be that triclabendazole acts on *F. hepatica* in a number of ways, or that it has a specific lethal action which is yet to be demonstrated.

The pharmacokinetics of albendazole (Marriner & Bogan, 1980), netobimin (Lanusse & Prichard, 1990), luxabendazole (Steel & Duwel, 1987), and triclabendazole (Hennessy *et al.*, 1987) have all been reported and the major pharmacokinetic parameters of the flukicidal benzimidazoles are given in Table II. The plasma pharmacokinetics of benzimidazoles are thought to be important for their efficacy against nematode parasites, and it is generally considered that persistence in the plasma is more important than the maximum drug concentration (C_{max}) or the total bioavailability (AUC) (Prichard *et al.*, 1978). The benzimidazoles with higher efficacy for gastrointestinal nematodes in ruminants are the least soluble drugs which are slowly absorbed and excreted from the rumen reservoir following oral administration. The major flukicidal benzimidazoles have relatively high C_{max} values and are all highly protein bound. The most effective drug against all stages of *F. hepatica* is triclabendazole, and this appears to be the most highly protein bound, a feature which may be important for drug uptake by the parasite. Albendazole and triclabendazole are both metabolized to their sulphoxide metabolites and since negligible amounts of the parent drug are found after oral administration they are assumed to undergo first pass oxidative metabolism in the liver (Marriner & Bogan, 1980; Hennessy *et al.*, 1987). The sulphoxide metabolites are thought to be the major active moieties and are to a large extent inactivated by further oxidation to the sulphone before excretion (Marriner, 1980). Low concentrations of albendazole have been detected in the plasma of sheep following the intraruminal administration of netobimin. It is subsequently oxidized to albendazole sulphoxide and sulphone as above (Delatour *et al.*, 1986). Luxabendazole is largely excreted unmetabolized in the faeces, although some unspecified metabolites are excreted in the urine (Steel & Duwel, 1987).

The benzimidazoles are relatively non-toxic drugs with very large therapeutic indices. However, some are known to be teratogenic. Albendazole has been shown to produce congenital malformations during early gestation in ewes and administration of high doses on day 17 appears to be particularly critical (Johns & Philip, 1977). In view of this care should be taken when using albendazole or its analogues at high dose rates in early pregnancy. Teratological studies of triclabendazole in rats did not reveal any evidence of embryotoxicity or fetotoxicity (Yoshimura, 1987).

Table II
Pharmacokinetic parameters of flukicidal benzimidazoles in sheep

	Dose given (mg/ml)	*Major metabolite for kinetic data*	C_{max} *(μg/ml)*	T_{max} *(h)*	*AUC (μg/ml)*	*Protein binding (%)†*
1* Albendazole	10	Albendazole sulphoxide	3.4	17	113	> 90
2* Netobimin (intraruminal)	20	Albendazole sulphoxide	2.4	17.5	95	> 90
3* Albendazole sulphoxide	5	Albendazole sulphoxide	1.9	9.3	40	> 90
4* Luxabendazole	10	Luxabendazole	0.5	20	30	95
5* Triclabendazole	10	Triclabendazole sulphoxide	13.3	18	424	99

*Authors: 1, Marriner & Bogan (1980); 2, Lanusse & Prichard (1990); 3, McKellar (unpublished results); 4, Steel & Duwel (1987); 5, Hennessy *et al.* (1987).

†Protein binding of albendazole metabolites has been shown to increase with time following administration of albendazole (Hennessy, 1985).

Because of their close relationship, albendazole, netobimin and albendazole sulphoxide are likely to have similar efficacies against flukes if given at doses which provide bioequivalent concentrations of the active drug, or the active metabolite. The dose rates of albendazole and netobimin have to be increased from 5 mg/kg to 7.5 mg/kg and 7.5 mg/kg to 20 mg/kg, respectively, for activity against *F. hepatica* in sheep and from 7.5 mg/kg to 10 mg/kg and 7.5 mg/kg to 20 mg/kg, respectively for *F. hepatica* in cattle. The dose of albendazole oxide (sulphoxide) must be increased from 5 mg/kg to 7.5 mg/kg for fluke in sheep. They are only useful for chronic fascioliasis since activity falls from approximately 95–100% for 15-week-old *F. hepatica* to 24–76% for 3-week-old *F. hepatica* (Knight & Colglazier, 1977). Albendazole sulphoxide has not yet got a product claim for *F. hepatica* in cattle, but is likely to be effective against adult fluke at a dose rate of 10 mg/kg in this species. These three drugs are all broad spectrum and have good activity against many gastrointestinal nematodes, lungworms and tapeworms in domestic animals (McKellar & Scott, 1990).

Luxabendazole also has broad spectrum of activity (Abbott, 1987) and in controlled tests against *F. hepatica* was shown to be 93–100% effective against 12-week stages, 72–99% effective against 8-week stages, and 30–92% effective against 6-week stages when given at 10 mg/kg body weight (Duwel, 1987). Triclabendazole has significant activity against fluke only (Coles, 1986). However, it is the only drug available which is highly effective against all stages of *F. hepatica.* In experimental infections it has been shown to be highly efficacious against fluke from 1 day old to 12 weeks old in sheep (Boray *et al.*, 1983; Turner *et al.*, 1984), and against immature flukes in goats (Kinabo & Bogan, 1988). Similarly, in field infections triclabendazole has also been shown to be extremely effective (Rapic *et al.*, 1984; Stansfield *et al.*, 1987). Triclabendazole is also effective against *F. gigantica* in sheep (Guralp & Tinar, 1984) and cattle and goats (Misra *et al.*, 1987), and against *Fascioloides magna* in calves (Craig & Huey, 1984). The high activity of triclabendazole against immature stages of *F. hepatica* and the relatively long prepatent period of the parasite may make strategic control of this parasite a realistic target. It has been suggested that a treatment during spring to reduce contamination of pastures with fluke eggs and then three treatments at 10-week intervals during the period of highest snail activity may be suitable (Wehrle & Richards, 1989). The authors point out that other susceptible host species may act as reservoirs of infection and where possible should be treated and that the programme may need to be adapted to local environmental situations.

SULPHONAMIDES

Clorsulon is only available in the UK in combination with ivermectin (Ivomec-F) as an injectible preparation for the treatment of cattle. It is a sulphonamide derivative with the chemical formula 4-amino-6-trichloroethenyl-1,3-benzendisulphonamide (Mrozik *et al.*, 1977). It acts on the parasite energy metabolism as a competitive inhibitor of 3-phosphoglycerate kinase and inhibits glucose oxidation to acetate and propionate, thereby blocking glycolysis and inhibiting ATP formation (Schulman & Valentino, 1980; Schulman *et al.*, 1982). It is thought that the parasites ingest clorsulon bound to host erythrocytes (Schulman *et al.*, 1979).

The pharmacokinetics of clorsulon have been assessed following subcutaneous administration to cattle, and it was found that a single dose of 4 mg/kg had a C_{max} of

2.42 μg/ml after 21.6 h, a terminal elimination half-life of 30 h and an AUC of 140 μg/ml/h, and that it was 94% protein bound in plasma (Mohammed-Ali, 1985). There is little information available on its use alone at 2 mg/kg which is the recommended dose for use in combination with ivermectin in the UK.

Clorsulon has a very wide therapeutic index in domestic animals (Ostlind *et al.*, 1977). It is highly effective against adult *F. hepatica* in cattle (de Leon & Quinone, 1983) and at 2 mg/kg has a 90% efficacy against 8-week-old immature fluke (Yazwinski *et al.*, 1985). In sheep an intraruminal administration of 2.5 mg/kg was shown to be more than 90% effective against adult and 6-week-old fluke (Mrozik *et al.*, 1977; Ostlind *et al.*, 1977) and at the very high dosage rate of 15 mg/kg has been shown to have 97% efficacy against 4-week-old fluke (Mrozik *et al.*, 1977).

In the UK a number of flukicidal drugs have been combined with nematodicidal drugs for the simultaneous treatment of fluke and worm infestation (Table III). These products are generally more effective against older parasitic stages of *F. hepatica* and are therefore more suitable for the treatment of subacute or chronic fascioliasis. It is also important to realize that the epidemiology of the major nematodes responsible for parasitic gastroenteritis is quite different from that of *F. hepatica* and often throughout the year one of the components is unnecessary when the other is essential. The prelambing dose often given to ewes to reduce or remove inhibited or recently ingested nematode parasites and chronic fluke burdens is a rational time to use the combination products.

Table III
Fluke and worm combination products

Trade name	*Flukicide*	*Nematodicide*	*Preparation*
Nilzan	Oxyclozanide	Levamisole	Drench
Spectril	Oxyclozanide	Levamisole	Drench
Worm Away	Oxyclozanide	Levamisole	Drench
Systamnex Plus Fluke	Oxyclozanide	Oxfendazole	Drench
Vermadex	Brotianide	Thiophanate	Drench
Flukombin	Brotianide	Thiophanate	Drench
Ranizole	Rafoxanide	Thiabendazole	Drench
Rycovet Duospec	Rafoxanide	Oxibendazole	Drench
Supaverm	Closantel	Mebendazole	Drench
Ivomec-F	Clorsulon	Ivermectin	Injection

Albendazole, albendazole oxide and netobimin have broad spectrum activity also.

In the UK, closantel, netobimin, albendazole sulphoxide, triclabendazole and clorsulon have all recently become available. The choice of a fasciolicidal drug will depend on the stage of the fluke infection, any concurrent parasitic burden and an observation of milk or meat withdrawal times (Table I) as well as the cost of the product and suitability of route of administration. It is important therefore to have a good knowledge of the pharmacology of the drugs available.

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