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PLASMA PROFILES OF ALBENDAZOLE METABOLITES AFTER ADMINISTRATION OF NETOBIMIN AND ALBENDAZOLE IN SHEEP: EFFECTS OF PARASITISM AND AGE

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SUMMARY

Netobimin and albendazole were administered to 3-month-old lambs with moderate infections of *Nematodirus battus* and to comparable parasite-naive lambs. Albendazole sulphoxide and albendazole sulphone concentrations were determined in the plasma of all lambs at frequent intervals after treatment. Both anthelmintic preparations were 100% effective in reducing nematode faecal egg output in the lambs. There were no significant differences in the concentrations of the sulphoxide or sulphone metabolites in parasitized compared with non-parasitized lambs given the same parent anthelmintic.

The parasite-naive lambs were subsequently weaned and maintained indoors in conditions designed to preclude nematode parasite infection until they were 9 months old. Netobimin and albendazole were administered again and the plasma profiles of the albendazole sulphoxide and albendazole sulphone metabolites determined. There were no significant differences in the plasma distribution of these metabolites with age of the lambs.

The area under the plasma concentration time curve, mean resident time and apparent half-life of the albendazole sulphoxide metabolite was determined following administration of each parent drug and the clearance of the metabolite/systemic availability of parent drug was determined as a marker of the amount of drug available for metabolism. There were no significant differences in pharmacokinetic variables between parasitized and non-parasitized animals nor with the age of the animals.

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INTRODUCTION

Following oral administration, netobimin, a nitrophenylguanidine prodrug of albendazole, is reduced by gut microflora and cyclized in the rumen or intestine (Delatour *et al.*, 1986). The albendazole thus formed is metabolized in the same way as parent albendazole and activity is attributed principally to the albendazole and albendazole sulphoxide metabolites. The major end product of oxidation is albendazole sulphone, which is thought to have little anthelmintic activity. The oral administration of albendazole to sheep results in very low concentrations of the parent sulphide in plasma but higher concentrations of the sulphoxide and sulphone metabolites. Extensive (first pass) oxidative metabolism is thought to occur in the liver after absorption and before entry into the systemic circulation (Marriner & Bogan, 1980).

The plasma kinetics and gastrointestinal distribution of some anthelmintics differ in parasitized and non-parasitized animals. The lower bioavailability of fenbendazole in sheep infected with *Ostertagia circumcincta* compared to non-parasitized sheep has been attributed to decreased solubility of the parent molecule in the abomasum since abomasal pH rises during *Ostertagia* infection. Metabolism of fenbendazole is also affected by abomasal parasitism since the proportion of parent compound relative to metabolite has been shown to be greater in parasitized than non-parasitized animals (Marriner *et al.*, 1985).

Intestinal parasitism may also affect the pharmacokinetics of anthelmintic drugs since the intestine is the major site of drug absorption and during nematode parasitism gut transit time may be reduced and intestinal villi may be atrophied (Coop *et al.*, 1973; Gregory *et al.*, 1985).

The pharmacokinetics of levamisole, ivermectin and netobimin have been studied in non-parasitized lambs and in lambs with a burden of *Nematodirus battus*. No significant differences in the bioavailability of the drugs between groups were detected (McKellar *et al.*, 1991) but the *N. battus* burdens in the parasitized lambs may have been too low to cause sufficient pathophysiological changes to affect the pharmacokinetics of the drugs.

Many other factors affect the pharmacodynamics and pharmacokinetics of drugs in animals and age is one variable which has been shown to have a pronounced effect. Absorption of anthelmintics is likely to be affected by age since the gastrointestinal tract in the young ruminant behaves as in monogastric animals until the rumen becomes fully functional at 8–12 weeks. The oesophageal groove may also act to bypass the rumen which normally slows the absorption of insoluble drugs such as the benzimidazoles. It is probable, however, that even when the reflex occurs, drug will remain spread along the oesophageal groove and omasum and will show a biphasic pattern of absorption (Bogan & Marriner, 1985).

Metabolism of drugs is also affected by age and hepatic development of metabolizing enzymes is thought to occur in a biphasic pattern. An initial period of 3–4 weeks of rapid development is followed by a slower period up to the tenth week of life (Baggot, 1977). Cytochrome P-450 enzymes of hepatic microsomes are important for oxidative metabolism of benzimidazole carbamates (Marriner, 1980) and development of these enzymes may be the rate-limiting step in metabolism as

animals age (Short & Davis, 1970). In calves, the half-life of antipyrine decreased in the order 26.94±9.07, 11.45±4.00, 7.30±1.83 and 3.97±0.61 h in 1-, 15-, 42-day-old and adult calves respectively (Depelchin, 1985). Other metabolic processes such as acetylation are thought to function at almost complete adult capacity in young animals (Vest & Rossier, 1963). Renal function may also affect drug disposition in the young animal since glomerular filtration rate is relatively inefficient, blood flow reduced and tubular secretion deficient (Goldstein *et al.*, 1974; Baggot, 1977). However, renal immaturity may not have a significant effect on drug disposition in lambs since some neonatal ruminant species (calves) have comparatively advanced renal function (Dalton, 1968) and although relatively deficient, the renal capacity of young animals may be quite sufficient to deal with the excretion of many drugs.

The mode of action of the benzimidazoles is thought to be by the inhibition of nematode tubulin formation and the period of exposure of parasite to the drug affects its efficacy. Since gastrointestinal and systemic concentrations of benzimidazoles are in equilibrium, greater persistence of systemic concentrations confers greater activity on the drug. Factors which affect absorption and plasma profiles of benzimidazoles are therefore important.

The present study was undertaken to determine whether the plasma profiles of albendazole metabolites altered following the administration of netobimin and albendazole in non-parasitized lambs and lambs infected with *N. battus*. Furthermore, the effect of age on the same plasma profiles was determined in non-parasitized lambs.

MATERIALS AND METHODS

Thirty-six Greyface Suffolk cross twin lambs which were born indoors in mid-March and reared indoors with their dams were used. Eighteen of the lambs with their dams were turned onto pasture contaminated with *N. battus* (Table I) on 10 April 1990. The remaining 18 lambs and their dams were reared indoors under conditions designed to reduce the likelihood of infection with gastrointestinal nematode parasites. Pasture larval samples were taken by the method of Taylor (1939) and the larvae recovered, counted and identified using the methods described by MAFF (1986). Faecal nematode egg output was determined weekly in the grazing lambs by a modification of the method of Christie & Jackson, (1982). All housed sheep had free access to water and were offered hay *ad libitum*. The lambs had access to creep feed *(ad libitum)* and the ewes were offered concentrate (0.5 kg/head/day).

Table I
Counts of *N. battus* (L_3) larvae on pasture (L_3/kg dried herbage)

Date	*11 April*	*9 May*	*23 May*	*6 June*
Count	382	127	248	120

All the lambs were allocated on 18 June into groups of six on the basis of sex, body weight (BW) and faecal egg count for the grazing lambs to produce balanced groups. One group from pasture and one housed group were treated orally on 19 June with each of the following anthelmintic drugs: netobimin (Hapadex Sheep Wormer; Schering Plough Animal Health) at a dose rate of 5.0 mg/kg; netobimin at a dose rate of 7.5 mg/kg; and albendazole (Valbazen 2.5% Total Spectrum Wormer; Smith Kline Beecham Animal Health) at a dose rate of 5.0 mg/kg. Syringes, of an appropriate size, were used to deliver the anthelmintics in the back of the pharynx and to ensure full delivery of the drug each syringe was rinsed with water. The lambs which had been on pasture were housed at the time of treatment and then kept indoors under the same conditions as the other lambs.

Blood samples were collected from the jugular vein from all lambs into lithium heparin vacutainers (Becton-Dickinson) before anthelmintic administration and at 2, 4, 8, 12, 20, 24, 36, 48, 72 and 96 h after treatment. Blood was centrifuged immediately at 1700 *g* and plasma collected and frozen at −20°C until the time of drug analysis.

The non-parasitized lambs were weaned on the day after the last blood sample was taken and were subsequently housed indoors on a maintenance ration under the same husbandry conditions as before, without their dams.

Netobimin and albendazole were administered at the same dose rates (in mg per kg body weight) to the same lambs 6 months later when the lambs were 9 months old. Blood samples were collected as before.

Analysis of plasma by high performance liquid chromatography for albendazole sulphoxide and albendazole sulphone was carried out by the methods of Bogan & Marriner (1980) and Marriner & Bogan (1980). Parent netobimin and albendazole were not analysed since they achieve negligible concentrations in plasma following oral administration in sheep (Marriner & Bogan, 1980; Delatour *et al.*, 1986).

The mean maximum plasma concentration (C_{max}) and time of C_{max} (t_{max}) were determined from observed values. The apparent half-life of the metabolite ($t_{\frac{1}{2}}(d)$) was obtained by least square regression analysis based on the decline phase of the plasma concentration–time curve. The area under the curve (AUC) was determined by the trapezoidal rule, the area of the terminal portion was estimated from the apparent elimination rate constant. Statistical moments analyses were used to determine the mean residence time (MRT), systemic clearance (CL) and availability (F) of the albendazole sulphoxide metabolite. The slow rate of formation of the albendazole sulphone meant that terms relating to its elimination could not be accurately determined. The AUC for this metabolite was determined using the trapezoidal rule.

Differences between pharmacokinetic parameters in parasitized and non-parasitized groups of sheep treated with the same parent drug were determined using a Mann–Whitney test and differences between the pharmacokinetic parameters with age in the same animals were determined using a Wilcoxon signed rank test. Results were considered significant when $P<0.05$.

RESULTS

Pasture *N. battus* larval counts ranged between 127 and 382 third-stage larvae (L_3) per kg dry herbage during the period that the lambs were grazing (Table I). The lambs on pasture became infected with *N. battus* and the geometric mean faecal *N. battus* egg counts are given in Table II. Treatment of lambs with netobimin and albendazole was 100% effective at reducing faecal *N. battus* egg counts. Faecal *N. battus* egg counts remained at zero 14 and 21 days after treatment.

The plasma concentrations of albendazole sulphoxide following administration of netobimin or albendazole in parasitized (previously on contaminated pasture) and non-parasitized (maintained indoors) lambs are shown in Figs 1 and 2 respectively. Figures 3 and 4 show the respective plasma comparisons for albendazole sulphone. The C_{max}, t_{max}, AUC, MRT, Cl/F and $t_{1/2}$ data for the albendazole

Table II
Geometric mean *N. battus* faecal egg counts in lambs grazing contaminated pasture

Group (n=6)	*Date*	*May*			*June*				*July*	
	Day after treatment	*9/5*	*16/5*	*23/5*	*6/6*	*12/6*	*19/6* *0*	*26/6* *7*	*3/7* *14*	*10/7* *21*
Netobimin										
5.0 mg/kg		15	149	102	186	74	121	0	0	0
7.5 mg/kg		61	95	182	182	186	299	0	0	0
Albendazole										
5.0 mg/kg		20	50	80	231	133	205	0	0	0

All lambs were housed and treated with anthelmintic on 19 June.

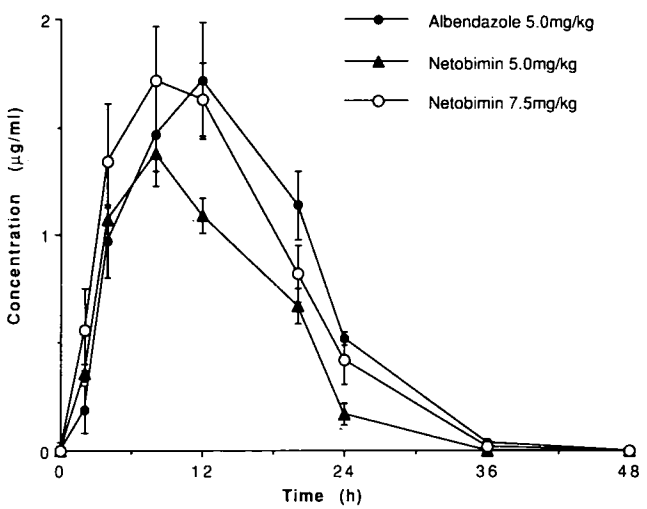

Fig. 1. Concentration (µg/ml) of albendazole sulphoxide in the plasma of parasitized sheep after administration of related anthelmintic preparations.

sulphoxide metabolite following each administration of anthelmintic are given in Table III. There were no significant differences in the pharmacokinetics of this metabolite between parasitized and non-parasitized animals, nor were there significant differences with age of the sheep.

The AUC values for albendazole sulphoxide following administration of netobimin at 7.5 mg/kg body weight (31.81±8.21 μg.h/ml) parasitized and 30.98±7.60 μg.h/ml) non-parasitized) were very similar to those achieved following adminis-

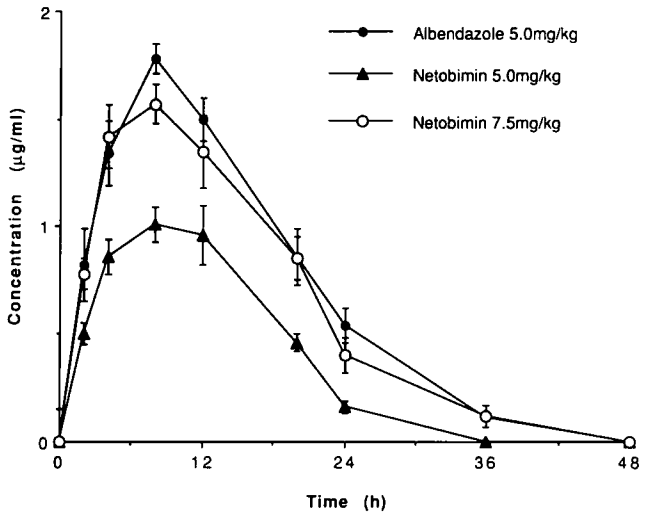

Fig. 2. Concentration (μg/ml) of albendazole suphoxide in the plasma of non-parasitized sheep after administration of related anthelmintic preparations.

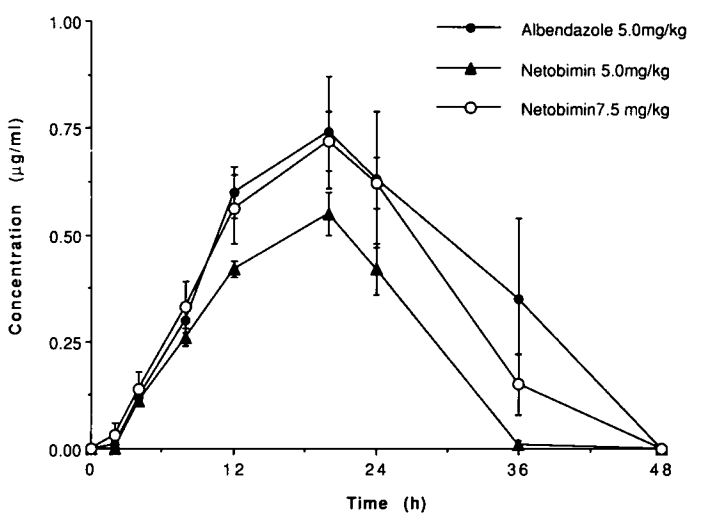

Fig. 3. Concentration (μg/ml) of albendazole sulphone in the plasma of parasitized sheep after administration of related anthelmintic preparations.

tration of albendazole at 5.0 mg/kg body weight (38.85±10.88 μg.h/ml) parasitized and 35.37±9.09 μg.h/ml) non-parasitized). These are the UK data sheet recommendations for these drugs. The C_{max}, t_{max} and AUC data for the albendazole sulphone metabolite following each administration of anthelmintic are given in Table IV.

The mean ratios of the AUC of albendazole sulphoxide to the AUC of albendazole sulphone were calculated for each preparation in parasitized and non-parasitized sheep to see whether parasitism affected oxidative metabolism (Table V). The ratios were smaller (i.e. relatively more sulphone compared to sulphoxide) in the parasitized than non-parasitized lambs given netobimin at either the 5.0 mg/kg or 7.5 mg/kg body weight, or albendazole at 5.0 mg/kg body weight. The non-parasitized lambs which were retreated when 9 months old gained weight between each part of the study and the mean weights are given in Table VI. The plasma concentration/time curves for albendazole sulphoxide and albendazole sulphone following administration of each related anthelmintic on the second occasion (9-month-old lambs) are given in Figs 5 and 6 respectively. The mean pharmacokinetic data for albendazole sulphoxide and albendazole sulphone are given in Tables III and IV respectively.

The plasma concentration versus time curves C_{max} and t_{max} values were similar in both parts of the experiment, indicating that the pattern of absorption of each anthelmintic preparation was similar in 3-month-old and 9-month-old lambs. There were no significant differences in pharmacokinetic values for albendazole sulphoxide for individual anthelmintic preparations on each occasion. There were also no significant differences in the ratios of albendazole sulphoxide:albendazole sulphone in the lambs following administration of either of the anthelmintic preparations on each occasion.

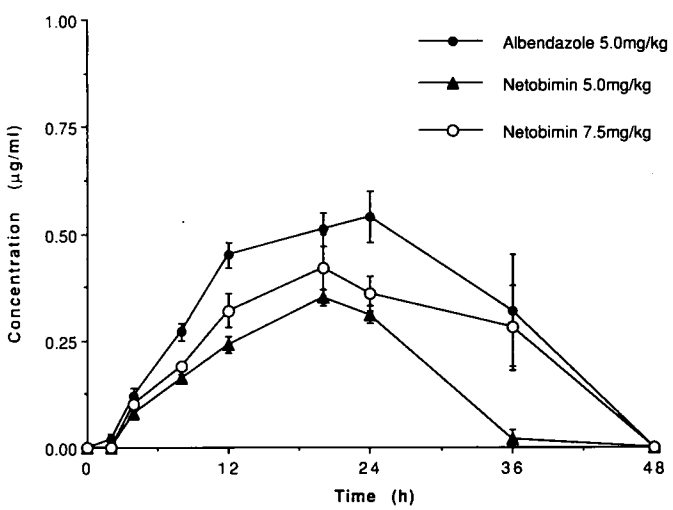

Fig. 4. Concentration (μg/ml) of albendazole sulphone in the plasma of non-parasitized sheep after administration of related anthelmintic preparations.

Table III
Pharmacokinetic parameters (mean±SD) for albendazole sulphoxide (metabolite) in sheep following administration of netobimin and albendazole

Age	*3 months*	*3 months*	*3 months*	*3 months*	*9 months*	*9 months*	*3 months*	*3 months*	*9 months*
Parasite status	*Non-parasitized*	*Non-parasitized*	*Parasitized*	*Parasitized*	*Non-parasitized*	*Non-parasitized*	*Non-parasitized*	*Parasitized*	*Non-parasitized*
Parent compound	*Netobimin*	*Netobimin*	*Netobimin*	*Netobimin*	*Netobimin*	*Netobimin*	*Albendazole*	*Albendazole*	*Albendazole*
Dose (mg/kg)	*5*	*7.5*	*5*	*7.5*	*5*	7.5	5	5	5
C_{max} (μg/ml)	1.12±0.25	1.62±0.25	1.39±0.17	1.93±0.51	1.10±0.37	1.76±0.29	1.83±0.27	1.81±0.54	1.30±0.12
t_{max} (h)	8.67±3.01	9.33±2.06	7.33±1.64	8.00±2.21	9.33±2.06	10.67±3.26	8.67±1.64	10.0±2.18	11.33±1.64
AUC μg.h/ml)	18.21±3.14	30.98±7.60	21.91±2.33	31.81±8.21	25.33±6.37	43.81±6.21	35.37±9.09	38.85±10.88	29.43±2.97
MRT(h)	12.81±2.51	14.53±2.81	12.91±1.56	14.06±2.85	17.13±2.31	18.67±1.29	15.69±4.90	17.42±7.46	19.81±4.44
CL/F [ml/(h·kg)]	281.2±46.6	255.3±65.7	230.5±25.6	249.5±63.8	206.9±47.3	173.8±22.3	147.7±30.2	135.6±31.3	171.4±18.0
$t_{1/2}$(d)(h)	6.37±1.89	7.69±1.91	6.36±1.64	6.74±1.58	8.67±2.29	8.66±1.98	7.88±3.74	8.25±5.51	9.57±4.49

Table IV
Pharmacokinetic parameters (mean±SD) for albendazole sulphone (metabolite) in sheep following administration of netobimin and albendazole

Age	*3 months*	*3 months*	*3 months*	*3 months*	*9 months*	*9 months*	*3 months*	*3 months*	*9 months*
Parasite status	*Non-parasitized*	*Non-parasitized*	*Parasitized*	*Parasitized*	*Non-parasitized*	*Non-parasitized*	*Non-parasitized*	*Parasitized*	*Non-parasitized*
Parent compound	*Netobimin*	*Netobimin*	*Netobimin*	*Netobimin*	*Netobimin*	*Netobimin*	*Albendazole*	*Albendazole*	*Albendazole*
Dose (mg/kg)	*5*	*7.5*	*5*	*7.5*	*5*	*7.5*	*5*	*5*	*5*
C_{max} (μg/ml)	0.36±0.05	0.45±0.17	0.55±0.12	0.76±0.15	0.41±0.12	0.48±0.45	0.57±0.12	0.90±0.17	0.44±0.74
t_{max}(h)	20.67±1.64	19.28±9.35	20.00±0.00	21.33±4.39	26.33±5.71	34.00±4.90	20.67±20.60	20.00±4.39	24.67±8.06
AUC μg.h/ml)	7.20±1.10	11.85±4.99	10.64±1.91	16.25±3.41	11.64±2.74	17.72±2.74	15.51±5.19	18.87±6.00	13.94±2.21

DISCUSSION

The *N. battus* faecal egg counts indicate that the lambs on pasture picked up a moderate or low infection. The counts never exceeded 300 eggs per gram of

Table V
Ratio of the mean AUC of albendazole sulphoxide to mean AUC of albendazole sulphone following administration of netobimin and albendazole

Parent compound Dose (mg/kg)	Netobimin 5	Netobimin 7.5	Albendazole 5
Ratio ABSX/ABSO in non-parasitized lambs	2.53	2.61	2.28
Ratio ABSX/ABSO in parasitized lambs	2.06	1.96	2.06

Table VI
Mean and standard errors of weights of lambs in groups given related anthelmintics on two occasions

		Lamb weights (kg)	
		Occasion 1 (3 months)	*Occasion 2 (9 months)*
Netobimin	5.0 mg/kg	25.2±2.2	32.1±1.2
Netobimin	7.5 mg/kg	25.4±2.7	31.8±2.9
Albendazole	5.0 mg/kg	25.2±2.2	32.8±2.1

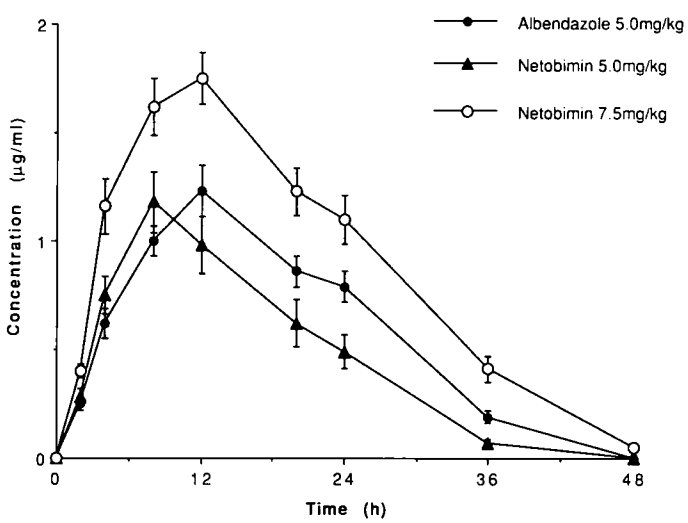

Fig. 5. Concentration (µg/ml) of albendazole sulphoxide in the plasma of 9-month-old sheep after administration of related anthelmintic preparations.

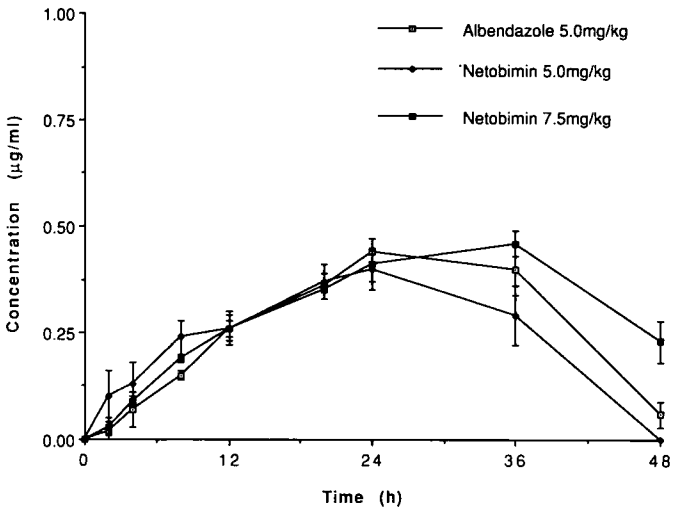

Fig. 6. Concentration (μg/ml) of albendazole sulphone in the plasma of 9-month-old sheep after administration of related anthelmintic preparations.

faeces and values of 1000–2000 are frequently obtained in severely infected animals (Kingsbury, 1953). Nevertheless, parasite burdens did become established and following treatment and housing nematode faecal egg counts decreased to zero in the groups administered netobimin and albendazole.

It has been demonstrated previously that following netobimin treatment an immediate drop in egg count may be followed by a subsequent small rise even when re-exposure to infective larvae is precluded (McKellar *et al.*, 1991). This has been attributed to poor efficacy against larval stages of *N. battus* or to temporary suppression of egg output by adult parasites. In the present study netobimin reduced the faecal egg output to zero without subsequent recurrence of egg output at days 7, 14 or 21 after treatment. Either the drug was completely effective against all stages of the parasite or the parasite burden present at the time of treatment had been acquired some time previously and no larval stages were present.

The plasma concentrations of albendazole sulphoxide achieved following administration of each preparation are important since the anthelmintic activity of each drug is thought to be principally associated with this moiety (Van den Bossche, 1985). The AUC values for albendazole sulphoxide following administration of netobimin at 5.0 mg/kg were lower than those following albendazole administered at 5.0 mg/kg. Lower concentrations of the metabolites of netobimin were expected since the prodrug has a larger molecular weight then albendazole, and since both preparations were given at the same dose in mg/kg, fewer molecules of netobimin were administered. Lower albendazole sulphoxide concentrations have been demonstrated previously in goats given netobimin compared to albendazole (Benchaoui *et al.*, in press). In the present study, when netobimin was administered at the dose rate recommended for sheep in the UK (7.5 mg/kg body weight) it produced remarkably similar concentrations of albendazole sulphoxide to albendazole, suggesting that both products would have similar anthelmintic activity.

There were no differences in the plasma profiles of the individual preparations in parasitized compared to non-parasitized animals, confirming previous results obtained with levamisole, ivermectin and netobimin in lambs with *N. battus* infections (McKellar *et al.*, 1991). There was a difference in the ratio of albendazole sulphoxide to albendazole sulphone in parasitized and non-parasitized lambs following administration of netobimin and albendazole. There was relatively more sulphone compared to sulphoxide in the parasitized lambs, suggesting greater hepatic sulphonating capacity. This is contrary to the results obtained by Marriner *et al.* (1985) who observed a reduction in the ratio of sulphonated metabolites following administration of fenbendazole to sheep infected with *O. circumcincta*. It seems unlikely that the differences in metabolic capacity of the lambs with the moderate infections experienced in the present study would prove clinically significant.

Comparing the same lambs aged 3 and 9 months, there were no significant differences in the plasma absorption of netobimin or albendazole administered orally. It is likely that a number of physiological developments occurred in the animals between each part of the study since the lambs were with their dams and still sucking during the first part whereas they were weaned and were larger (approximately 7 kg) during the second part of the study. It is possible that significant differences would have been observed if the first part of the study had been carried out in much younger lambs. However, it is less common for very young lambs to be treated with anthelmintic unless exposed to severe *N. battus* infection. Nevertheless, younger lambs are treated with anthelmintic on commercial farms and there is a paucity of data on the age-related kinetics in these groups.

In the present study netobimin was given at two different dose rates, the lower dose (5.0 mg/kg) was designed to permit comparison of the plasma profile of the sulphoxide metabolite when given at the same dose as albendazole. The higher dose was given to determine the kinetics following the recommended therapeutic dose for sheep of the netobimin preparation used. In the present study the AUC data of albendazole sulphoxide following administration of either dose of netobimin compared favourably with corresponding data for albendazole.

In conclusion, low or moderate burdens of *N. battus* are unlikely to affect the absorption or metabolism of netobimin or albendazole in any way which would adversely affect their clinical efficacy. Furthermore the physiological changes which occur with age in lambs from 3 (unweaned) to 9 months old (weaned) do not affect the absorption or distribution of netobimin or albendazole.

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