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Influence of Diet Type and Pretreatment Fasting on the Disposition Kinetics of Albendazole in Sheep

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ABSTRACT

The influence of the quality and quantity of diets on the disposition kinetics of albendazole were studied in sheep in two different experiments. The plasma concentration profiles of albendazole sulphoxide and albendazole sulphone were measured following intraruminal administration of albendazole at 5.0 mg/kg body weight in weaner sheep offered three different diets: 100% green *Sorghum* spp., 100% dry mature *Cenchrus ciliaris* hay and a 50:50 mix of these two diets. The peak plasma concentrations and the availability of the albendazole metabolites, as measured by the area under the concentration–time curve, were significantly higher ($p<0.01$) in the animals offered exclusively dry fodder compared to other diets. Changing the diet from dry to green fodder resulted in a significantly lower systemic availability of the drug metabolites. It is suggested that a decreased transit time of the digesta in the bowel on the green diet, with its high water content, limited the systemic availability of the drug by reducing the time available for gastrointestinal absorption.

An experiment on the influence of different levels of pretreatment fasting on the pharmacokinetics of albendazole revealed significantly higher ($p<0.05$) plasma concentrations of the anthelmintically active sulphoxide metabolite from 12 h onwards following administration of the drug in animals subjected to 24 h of pretreatment fasting compared to other groups with pretreatment fasting of 8, 12 or 18 h. The area under the concentration–time curve and the minimum residence time of the drug metabolites were significantly greater ($p<0.05$) in animals that had been fasted for 24 h. It is suggested that fasting induces a decrease in the flow of digesta through the gastrointestinal tract of ruminants and prolongs the duration of dissolution of the drug, resulting in enhancement of the absorption of albendazole and of the systemic availability of its metabolites.

Keywords: albendazole, diet, fasting, green fodder, pharmacokinetics, sheep

Abbreviations: ABZ, albendazole; ABZ-SO, albendazole sulphoxide; ABZ-SO_2, albendazole sulphone; AUC, area under concentration–time curve; C_{max}, concentration maximum of ABZ metabolites in plasma; DMSO, dimethyl sulphoxide; ETH-OFZ, ethyl oxfendazole; FBZ, fenbendazole; HPLC, high-performance liquid chromatography; MRT, mean residence time; OFZ, oxfendazole; T_{max}, time to reach C_{max}; $t_{\frac{1}{2}\alpha}$, absorption half-life; $t_{\frac{1}{2}\beta}$, elimination half-life

INTRODUCTION

ABZ (methyl [5-(propylthio)-1*H*-benzimidazol-2-yl] carbamate), a member of the benzimidazole group of anthelmintics, is highly effective at different dose rates against

all stages of gastrointestinal nematodes, including lungworms, and against cestodes and adult liver flukes in cattle, sheep and goats (Theodorides *et al.*, 1976). Because of its aliphatic side-chain, ABZ is more quickly metabolized in the liver following absorption than are other sulphide benzimidazoles (Hennessy *et al.*, 1989), and its two metabolites, ABZ-SO and ABZ-SO_2 appear and are eliminated more quickly from the vascular compartment, with a reduced area under the concentration–time curve (Sanyal, 1997, 1998), compared to other sulphide benzimidazoles with an aromatic side-chain, such as FBZ (Sanyal, 1994).

As a class, benzimidazole anthelmintics are deposited in the rumen following oral administration in ruminants and become associated with the particulate digesta, being then released slowly to the liquid phase for absorption through the absorptive surfaces of the gastrointestinal tract (Hennessy *et al.*, 1994). Following hepatic metabolism, the active metabolite and/or the parent drug undergo prolonged recycling between the enteral and parenteral tissues (Hennessy, 1997). This recycling is of great pharmacological importance since the efficacy of benzimidazole anthelmintics is greatly influenced by the duration of their systemic availability (Prichard *et al.*, 1978; Hennessy, 1994).

It is well recognized that altering the quantity and quality of the diet changes the gastrointestinal transit time of digesta in ruminants and may therefore influence the time available for absorption of a drug (Warner, 1981). Research results, reviewed by Hennessy (1997), have indicated that, during the association and dissociation process undergone by benzimidazole anthelmintics in the rumen following oral administration, the systemic availability of the drug is significantly influenced by the rate of passage of the digesta. Variations in the quality (Taylor *et al.*, 1992; Sanyal *et al.*, 1995; Knox and Steel, 1997) and quantity (Ali and Hennessy, 1993, 1995; Sanchez *et al.*, 1997; Lifschitz *et al.*, 1997) of fodder offered may therefore produce major changes in the systemic availability of benzimidazole anthelmintics in sheep, cattle and buffaloes.

The present study investigated, in two different experiments, the effects of changing the proportion of two locally available green and dry fodders in the diet of sheep and of different periods of fasting on the disposition of ABZ metabolites in plasma. This was designed to ascertain the likely influence of such feed resources on the efficacy of anthelmintic treatment in small ruminants in India.

MATERIALS AND METHODS

Location and climate

The study was conducted at the Central Sheep and Wool Research Institute, Avikanagar, Rajasthan, where the sheep flocks are semi-intensively managed. The study area has been agroclimatically classified as semi-arid, with a mean annual rainfall of 600 mm.

Experiment on diet type

Fifteen 4–5-month-old weaner sheep, weighing 10.5–23.0 kg were housed and treated with 15.0 mg/kg body weight of tetramisole. Their freedom from nematode parasites was confirmed by repeated faecal examination. After a washout period of 15 days, the animals were divided into three equal groups: group 1, offered an *ad libitum* diet of 100% freshly cut green Jowar (*Sorghum* spp.) and water ($n = 5$); group 2, offered an *ad libitum* diet of 100% *Cenchrus ciliaris* hay and water ($n = 5$); group 3, offered an *ad libitum* diet of a 50:50 mixture of green *Sorghum* and *Cenchrus* hay and water ($n = 5$).

Following acclimatization to their diets for a period of 7 days, all the animals were given an intraruminal injection of ABZ (Smith Kline Beecham India Ltd, Bangalore, India) at 5.0 mg/kg body weight.

Experiment on pretreatment fasting

Sixteen weaner sheep, of about the same age and body weight as in the previous experiment, were maintained on *Cenchrus ciliaris* hay and water *ad libitum*, supplemented with 240 g concentrate feed per animal per day. They were also treated with tetramisole and their freedom from parasites was confirmed by repeated faecal examination. After a washout period of 15 days, the animals were divided into four equal groups: group 1, pretreatment fasting for 8 h ($n = 4$); group 2, pretreatment fasting for 12 h ($n = 4$); group 3, pretreatment fasting for 18 h ($n = 4$); group 4, pretreatment fasting for 24 h ($n = 4$).

Following the pretreatment fast, all the animals were given an intraruminal injection of ABZ (Smith Kline Beecham India Ltd) at 5.0 mg/kg body weight.

Samples

Blood was collected by jugular venepuncture into heparinized vials (Vacutainer, Becton Dickinson Inc., CA, USA) at 0, 2, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48 and 72 h after dosing with ABZ. The plasma was separated immediately by centrifugation and stored at –20°C until analysed by HPLC (Sanyal, 1997).

Reagents

Pure standards of ABZ, ABZ-SO and ABZ-SO_2 were supplied by Smith Kline Beecham India Ltd. Ethyl oxfendazole (ETH-OFZ), used as an internal standard, was supplied by Dr D.R. Hennessy, CSIRO McMaster Laboratory, Sydney, Australia.

Plasma extraction

Solid-phase extraction of the plasma (Hennessy *et al.*, 1985) was done using a C18 Sep-pak (Waters Associates, Millford, MA, USA). Plasma (1 ml) was spiked with 0.5 μg ETH-OFZ internal standard and applied to a C18 Sep-pak cartridge that had been preconditioned with 10 ml HPLC-grade methanol and 5 ml Sep-pak buffer. Following elution with 10 ml water and 0.5 ml 40% methanol, the metabolites were collected in 2.5 ml methanol and evaporated under nitrogen gas to approximately 300 μl before HPLC analysis.

HPLC analysis

The reversed-phase HPLC (System Gold, Beckman Instruments Inc., San Ramon, CA, USA) consisted of a 126 programmable solvent module, manual injector, 166 programmable detector module set at 292 nm, and a C18 4 μm Radial-pak column contained in a radial compression module (RCM, Waters Associates). The system was run in the isocratic mode using 33% acetonitrile in 0.025 mol/L sodium acetate as the mobile phase (Sanyal, 1997). Identification of the metabolites in plasma was done by comparison with the retention times of the reference standards. The absolute recovery rate was 97%, the precision of the extraction procedure and chromatography being evaluated by processing, as replicates on different days, pooled plasma aliquots containing known amounts of ABZ-SO and ABZ-SO_2.

Preparation of the standard curve

Stock solutions of ABZ-SO, ABZ-SO_2 and ETH-OFZ were prepared in DMSO at a concentration of 1000 μg/ml. Working solutions of 0.125, 0.25, 0.5 and 1.0 μg/5 μl (external standards) were prepared in DMSO from the stock solutions. Blank plasma (1 ml) was spiked with the external standards at five different concentrations of 0, 0.125, 0.25, 0.5 and 1.0 μg/ml and 0.5 μg of the internal standard ETH-OFZ was added to each vial. The spiked plasma was extracted by solid-phase extraction and dried down to 300 μl under nitrogen gas. Then, 15 μl was injected into the column to enable calibration curves to be prepared for the two components. The concentrations of each component in the plasma extracts were determined by comparing the detector response for each component with the corresponding peak in the standard mixture. Least-squares regression analysis was used to determine the slope, intercept and correlation coefficient for each compound in the concentration range tested. The limit of detection was 0.03 μg/ml.

Kinetic and statistical analysis

The C_{max}, T_{max}, AUC and $t_{\frac{1}{2}}$ for ABZ-SO and ABZ-SO_2 were determined using the nonlinear modeling program PHARMKIT, which fitted the concentrations versus time profiles to a first-order input and output, two-compartment model (Sanyal, 1994).

The plasma concentrations and kinetic values were compared for significance between the groups using one-way analysis of variance and the nonparametric Tukey–Kramer multiple range test, respectively, using Instat software (GraphPad Software Inc., San Diego, CA, USA, 1990–1994).

RESULTS

Experiment on diet type

The mean plasma disposition profiles of ABZ-SO and ABZ-SO_2 and their mean pharmacokinetic parameters are presented in Figures 1 and 2 and Table I, respectively. Analysis of the data revealed significantly higher ($p < 0.05$) plasma concentrations of ABZ-SO 2 h after ABZ administration in the mixed and dry fodder groups compared to the animals with access to 100% green fodder. At 10 and 12 h after administration of the drug, the concentration of the sulphoxide metabolite remained significantly higher ($p < 0.05$) in the plasma of the dry fodder group (1.91 ± 0.17 and 1.98 ± 0.10 μg/ml) compared to those offered mixed fodder (1.29 ± 0.10 and 1.34 ± 0.08 μg/ml). ABZ-SO_2 appeared more slowly in the plasma and never reached such high concentrations as

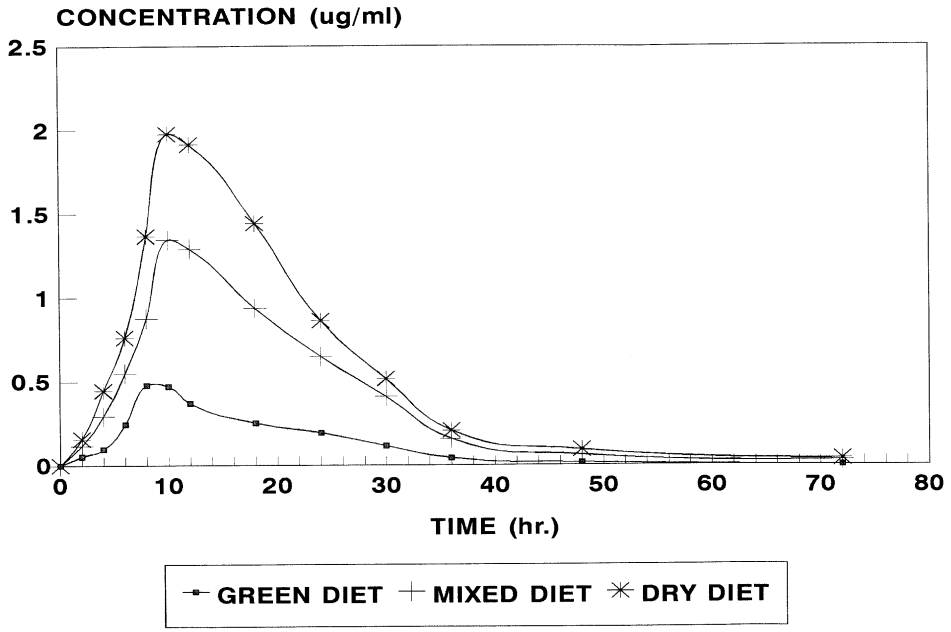

Figure 1. Plasma concentrations (mean ± SD) of albendazole sulphoxide (ABZ-SO) in sheep with access to three different diet types, following intraruminal administration of a single therapeutic dose of albendazole at 5.0 mg/kg body weight

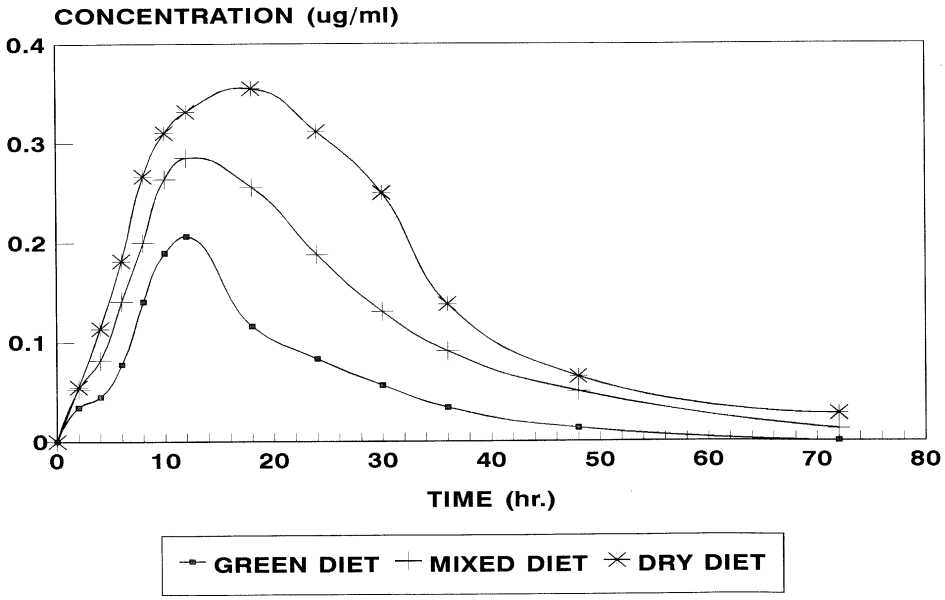

Figure 2. Plasma concentrations (mean ± SD) of albendazole sulphone (ABZ-SO_2) in sheep with access to three different diet types, following intraruminal administration of a single therapeutic dose of albendazole at 5.0 mg/kg body weight

ABZ-SO, but both were significantly higher ($p < 0.05$) in the sheep fed on dry fodder 24–36 h after administration than in the sheep fed on the other two diets. The ratio of ABZ-SO in plasma for dry:mixed:green diets was 1.00:0.68:0.24 and that for ABZ-SO_2 was 1.00:0.73:0.41.

A comparison of the mean C_{max} for both ABZ-SO and ABZ-SO_2 across all the groups revealed a significant effect ($p < 0.05$) of diet. Animals offered 100% dry fodder had the highest C_{max} value followed by those offered the mixed diet (Table I). The mean T_{max} for ABZ-SO was significantly higher ($p < 0.05$) for the dry and mixed fodder groups compared to the green fodder group, while for ABZ-SO_2 it was similar for all the groups. The mean AUC values for both metabolites were significantly influenced by the type of diet, being greatest in the animals on the dry diet and least in those on the green diet (Table I). There were no marked effects on mean $t_{\frac{1}{2}\alpha}$ or $t_{\frac{1}{2}\beta}$ from the different diets. The MRT of both metabolites was significantly lower ($p < 0.05$) in the animals fed on the 100% green diet.

TABLE I
Pharmacokinetic parameters (mean ± SD) of albendazole sulphoxide (ABZ-SO) and albendazole sulphone (ABZ-SO_2) in sheep with access to three different diets

Diet	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-0} (μg.h/ml)	$t_{\frac{1}{2}\alpha}$ (h)	$t_{\frac{1}{2}\beta}$ (h)	MRT (h)
ABZ-SO						
Green	$0.57^{a} \pm 0.20$	$8.80^{a} \pm 0.98$	$8.25^{a} \pm 3.49$	$4.46^{a} \pm 0.89$	$7.55^{a} \pm 0.91$	$17.54^{a} \pm 1.86$
Mixed	$1.38^{b} \pm 0.17$	$10.40^{b} \pm 0.80$	$26.54^{b} \pm 2.69$	$5.52^{b} \pm 0.20$	$7.72^{a} \pm 0.77$	$20.18^{b} \pm 1.54$
Dry	$2.09^{c} \pm 0.29$	$10.80^{b} \pm 0.98$	$38.22^{c} \pm 7.56$	$5.34^{a} \pm 0.73$	$7.43^{a} \pm 0.71$	$19.50^{b} \pm 1.04$
ABZ-SO_2						
Green	$0.23^{a} \pm 0.08$	$10.80^{a} \pm 1.60$	$4.12^{a} \pm 1.23$	$5.36^{a} \pm 0.92$	$10.29^{a} \pm 1.73$	$21.75^{a} \pm 3.28$
Mixed	$0.31^{a} \pm 0.04$	$12.80^{a} \pm 2.71$	$8.19^{b} \pm 0.90$	$6.11^{a} \pm 0.97$	$11.41^{a} \pm 1.43$	$26.13^{b} \pm 2.56$
Dry	$0.40^{b} \pm 0.05$	$14.40^{a} \pm 4.45$	$11.96^{c} \pm 1.53$	$6.30^{a} \pm 1.61$	$13.03^{b} \pm 1.64$	$28.17^{b} \pm 1.76$

C_{max}, concentration maximum; T_{max}, time to reach C_{max}; AUC, area under concentration–time curve; $t_{\frac{1}{2}\alpha}$, absorption half-life; $t_{\frac{1}{2}\beta}$, elimination half-life; MRT, mean residence time

[a,b,c]Means of pharmacokinetic parameters with different superscripts between the diet groups within the same metabolite were significantly different ($p < 0.05$)

Experiment on pretreatment fasting

The plasma concentrations of ABZ-SO were significantly higher from 12 h onwards following administration of the drug in animals subjected to 24 h fasting compared to the other groups. ABZ-SO_2 appeared more slowly in the plasma and, unlike ABZ-SO, never reached very high concentrations in any of the groups. However, its plasma concentrations were significantly higher ($p < 0.05$) at 24–30 h in the group fasted for 24 h. From 2 to 72 h following ABZ administration, the ratios of total available ABZ-SO and ABZ-SO_2 in the 24:18:12:8 h fasting groups were 1.00:0.72:0.67:0.59 and 1.00:0.75:0.79:0.69, respectively. The higher AUC value for ABZ-SO in the sheep subjected to a 24 h pretreatment fast compared to other fasting schedules suggests a linear correlation between the kinetics of ABZ metabolites and duration of pretreatment fasting.

The mean plasma disposition profiles of ABZ-SO, ABZ-SO_2 and their mean pharmacokinetic parameters are presented in Figures 3 and 4 and Table II, respectively. No difference in C_{max}, T_{max} or $t_{\frac{1}{2}\beta}$ was observed between the groups. However, the $t_{\frac{1}{2}\alpha}$, AUC and MRT of ABZ-SO were significantly higher ($p < 0.05$) in animals subjected to pretreatment fasting for 24 h than those for the animals fasted for 8 h.

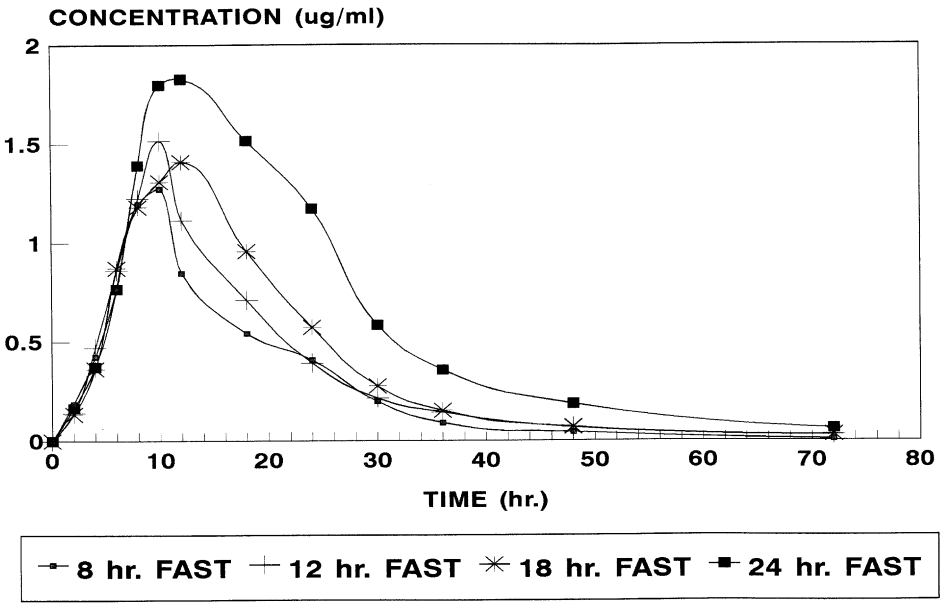

Figure 3. Plasma concentrations (mean ± SD) of albendazole sulphoxide (ABZ-SO) in sheep subjected to different levels of pretreatment fasting, following intraruminal administration of a single therapeutic dose of albendazole at 5.0 mg/kg body weight

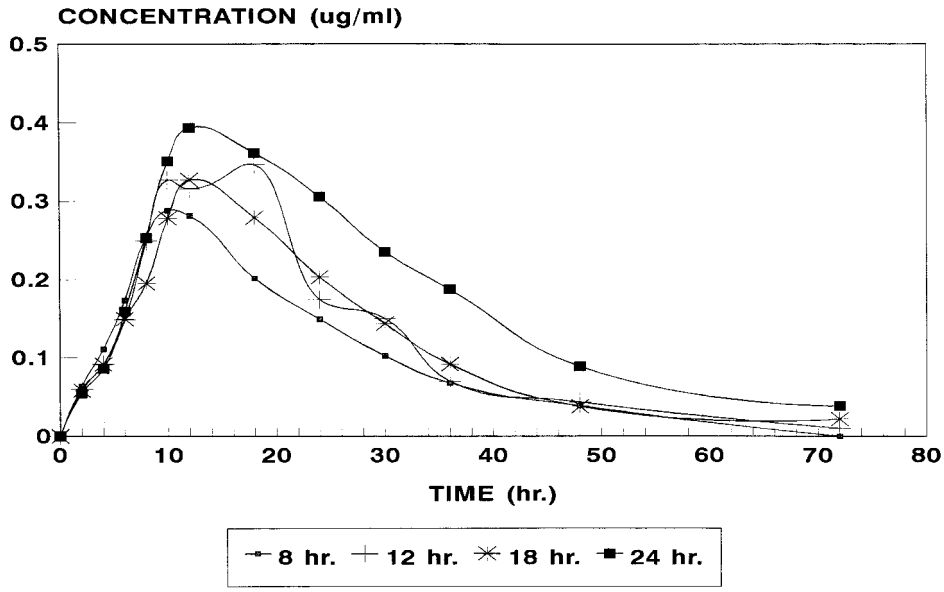

Figure 4. Plasma concentrations (mean ± SD) of albendazole sulphone (ABZ-SO_2) in sheep subjected to different levels of pretreatment fasting, following intraruminal administration of a single therapeutic dose of albendazole at 5.0 mg/kg body weight

DISCUSSION

Experiment on diet type

There was a substantial reduction in the systemic availability of both ABZ metabolites in animals offered 100% fresh *Sorghum* green fodder compared to those maintained on 100% dry, mature *Cenchrus* hay. A similar trend in drug bioavailability with diet changes was observed in sheep by Taylor and colleagues (1992) and in cattle and buffaloes by Sanyal and colleagues (1995). Alwash and Thomas (1971) reported that a diet's physical form may affect both its digestibility and the rate of flow of digesta in the gastrointestinal tract. Though the flow rate of the digesta in the intestine was not measured in the present experiment, it is well established that, as diet quality improves and intake increases, the residence time of the digesta in the gastrointestinal tract decreases (Warner, 1981). The reduced systemic availability of ABZ metabolites in sheep with access to 100% green fodder observed in the present study accorded with the observations of Taylor and colleagues (1992), who reported reduced bioavailability of FBZ and its metabolites in sheep and cattle grazing on pasture compared to those confined and offered hay and concentrate feed. This may be the result of increased digesta flow rates in the animals consuming green food, with the resultant decreased residence time of the drug in the gastrointestinal tract affecting its absorption.

TABLE II
Pharmacokinetic parameters (mean ± SD) of albendazole sulphoxide (ABZ-SO) and albendazole sulphone (ABZ-SO_2) in sheep with different levels of pretreatment fasting

Fasting (h)	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-0} (μg.h/ml)	$t_{\frac{1}{2}\alpha}$ (h)	$t_{\frac{1}{2}\beta}$ (h)	MRT (h)
ABZ-SO						
8	1.46 ± 0.08	9.00 ± 1.00	19.87[a**] ± 3.02	3.16 ± 0.25	7.81 ± 2.17	16.91 ± 2.08
12	1.51 ± 0.11	10.22 ± 0.80	23.79[a**] ± 5.13	3.73 ± 0.62	7.13 ± 1.49	18.13 ± 3.29
18	1.71 ± 0.21	10.50 ± 1.66	27.59[a*] ± 7.79	4.36 ± 1.28	7.15 ± 0.31	18.76 ± 1.34
24	1.89 ± 0.35	11.00 ± 1.00	43.92[b] ± 5.56	5.97 ± 1.28	9.05 ± 1.09	22.71 ± 2.27
ABZ-SO_2						
8	0.30 ± 0.03	10.50 ± 0.87	7.18 ± 0.73	4.55 ± 1.45	11.10 ± 1.49	23.39 ± 2.78
12	0.45 ± 0.17	14.50 ± 3.57	8.99 ± 2.84	5.39 ± 0.73	10.90 ± 2.41	23.73 ± 4.06
18	0.34 ± 0.05	11.50 ± 0.87	8.54 ± 1.88	6.25 ± 1.20	10.48 ± 2.39	24.57 ± 3.14
24	0.45 ± 0.08	16.50 ± 4.97	12.97 ± 1.43	7.52 ± 1.88	12.69 ± 0.76	29.62 ± 1.77

C_{max}, concentration maximum; T_{max}, time to reach C_{max}; AUC, area under concentration–time curve; $t_{\frac{1}{2}\alpha}$, absorption half-life; $t_{\frac{1}{2}\beta}$, elimination half-life; MRT, mean residence time

[a,b]Means of pharmacokinetic parameters with different superscripts between the pretreatment groups within the same metabolite were significantly different (*$p < 0.05$; **$p < 0.01$)

The significantly higher ($p<0.05$) AUC and C_{max} of ABZ-SO and AUC of ABZ-SO_2 in animals offered 100% dry fodder compared to those offered the mixed or 100% green diets (Table I) reflected the higher uptake of anthelmintic in the sheep offered the dry diet. The significantly higher ($p<0.05$) T_{max} of ABZ-SO in sheep on dry and mixed diets compared to the group on the green diet suggests differing availability of the drug at the absorption sites. However, Ali and Chick (1992) observed no difference in the T_{max} of OFZ in sheep offered different types of feed. The significantly lower ($p<0.05$) MRT in animals fed on 100% green fodder reflected the decreased drug absorption and recycling (Hennessy, 1993) caused by the shorter gastric transit time in sheep on a high feed intake, particularly of fresh feed with a high water content.

Experiment on pretreatment fasting

Lanusse and colleagues (1994) reported that starvation modifies the disposition kinetics of ABZ in the plasma of cattle. Lifschitz and colleagues (1997) observed that pretreatment fasting induced marked alterations in the kinetics and bioavailability of ABZ metabolites in sheep.

Fasting induces a decrease in the flow rate of the digesta through the gastrointestinal tract of ruminants. Decreased gastrointestinal absorption of OFZ in sheep with a high feed intake has been related to a shorter gastrointestinal transit time and hence less time for drug desorption from particulate material in the rumen (Ali and Hennessy, 1995). This slower rate of passage of the ruminal contents could prolong the duration of the desorption process, resulting in enhanced absorption of ABZ. The higher peak plasma concentration of both the metabolites and the significantly higher AUC observed in the present study when animals were fasted for longer periods prior to treatment tend to confirm such increased absorption.

The diet's physical form may affect the digestibility and rate of flow through the gastrointestinal tract and the ability of dietary cellulose to bind with the drug (Bogan and Marriner, 1987). Both these factors may contribute to the differences in pharmacokinetic behaviour of ABZ metabolites and in the therapeutic efficacy of the drug (Arundel, 1983). The influence of the type of diet has often been overlooked when determining anthelmintic efficacy. The results of the present study suggest that studies should include this factor in assessing dose response to avoid underdosing and reduced anthelmintic efficacy. Restricting the intake of feed is another way to manipulate the host's physiology and improve absorption of benzimidazole anthelmintics from the ruminant gastrointestinal tract, so enhancing its systemic availability and efficacy (Hennessy, 1993). The results of the present study suggested that a 24 h pretreatment fasting enhances absorption of ABZ.

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