Eur J Clin Pharmacol (1986) 30: 705-708

European Journal of Clinical Pharmacology

Pharmacokinetics of Albendazole in Man

S. E. Marriner[1], D. L. Morris[2], B. Dickson[3], and J. A. Bogan[1].

[1] Department of Veterinary Pharmacology, University of Glasgow Veterinary School, Bearsden, Glasgow
[2] The General Hospital, Birmingham
[3] Overseas Medical Division, Smith, Kline and French Laboratories, Welwyn Garden City, Herts, UK

Summary. The pharmacokinetics of albendazole were investigated in healthy volunteers and in patients receiving albendazole for treatment of hydatid disease. Unchanged albendazole was below detectable limits in plasma, urine, bile and cyst fluid. The major metabolite present in all fluids was the sulfoxide. Maximum concentrations of albendazole sulfoxide in plasma were very variable, probably due to variable absorption of albendazole.

Key words: albendazole, hydatid disease; pharmacokinetics, man

The pharmacokinetics of albendazole, a potent benzimidazole anthelmintic, have been described in a number of species [1, 2]. There is little data available on the pharmacokinetics of this drug in man although it is now widely available in many countries for the treatment of the gastro-intestinal helminthiases in man, and has shown evidence of good efficacy in the treatment of hydatid cysts in man [3]. The present work describes the pharmacokinetics of albendazole in normal human volunteers and in patients undergoing treatment for hydatid disease. Since there is evidence that absorption of the related benzimidazole mebendazole is altered by its incorporation into a fatty meal [4], an additional investigation of the effect of fat on the absorption of albendazole was also carried out.

Materials and Methods

Ten normal human volunteers, 5 female (age 18-25 years, mean body weight 58.7 kg, range 51.0-65.5 kg) and 5 male (age 26-37 years, mean body weight 76.0 kg, range 68.0-85.0 kg) clinically healthy, free of helminth infection, and not receiving any other drugs, were given a single oral dose of 400 mg albendazole (2 × 200 mg tablets 'Zentel'; Smith, Kline & French) after a 12 h overnight fast. Food was withheld for a further 4 h after drug administration when a light meal was provided.

Blood samples were taken prior to drug administration and at 0.5, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 24 and 32 h after drug administration. After centrifugation and separation from cells, the plasma was stored at −20 °C until analysis for albendazole and its major metabolites.

Clinical Study

Five patients, 2 male and 3 female, hospitalised for therapy of hydatid disease, were treated at a dose rate of approximately 10 mg/kg/day of albendazole in 3 divided doses. Blood was taken for estimation of the plasma concentration of albendazole and its major metabolites at various intervals over the initial 24 h period of therapy. In 2 of the 5 patients, there was parasite involvement only in the liver, in 2 others there was multi-organ involvement and in the fifth patient the cysts were in the peritoneal cavity.

In 3 other patients, samples of hydatid cyst fluid were obtained; in 2 cases from the main cyst and in one from intact daughter cysts within the main cyst. In one of these patients bile samples were obtained over a period of 6 h after surgical removal of cysts from the common bile duct. Cyst fluid and bile were stored at −20 °C until analysed.

Effect of Fat on Absorption of Albendazole

Four human volunteers, 3 male and 1 female, were given a single dose of 400 mg albendazole (2 ×

200 mg tablets) on two occasions; after an overnight fast, as in the first study, and 2 weeks later with 20 ml of olive oil in 100 ml milk. Blood samples were taken prior to drug administration and at 1, 2, 3, 4, 6, 8 and 24 h after dosing. In the first part of this study total urine volume voided from 0–4 h, 4–8 h and 8–24 h, was recorded. Aliquots of urine were stored at −20 °C until analysed.

Analysis of Samples

Analysis of plasma, bile, urine and hydatid cyst fluid for albendazole and its two major metabolites, albendazole sulfoxide and albendazole sulfone, was by high performance liquid chromatography separation of an ether extract [5] and was performed within 6 weeks of the samples being taken. The limit of detection of the HPLC method was 0.04 μg/ml for albendazole sulfoxide and 0.02 μg/ml for albendazole and albendazole sulfone. Standard samples of plasma fortified with 0.1–2.0 μg/ml of albendazole sulfoxide were used for recovery determination. Quality control of the method revealed an intra-assay coefficient of variation of 4.52% on analysis of 20 plasma samples having a mean sulfoxide concentration of 0.42 μg/ml (range 0.08–1.82 μg/ml) analysed in duplicate. The inter-day coefficient of variation determined on plasma samples fortified at 0.1 and 0.8 μg/ml was 5.11% and 5.01% respectively. Urine samples were also examined by thin layer chromatography (TLC) using the method of Gyurik [2] to determine whether there were substantial amounts of albendazole metabolites other than albendazole sulfoxide and albendazole sulfone.

Pharmacokinetic Analysis

Area under the plasma concentration-time curve (AUC) was determined using the trapezoidal rule. Renal clearance of sulfoxide was determined using the formula $CL_R = \frac{U}{AUC}$ where CL_R = renal clearance and U = the total amount of sulfoxide excreted in urine.

Results

The concentrations of albendazole and of albendazole sulfone were below detectable limits (0.02 μg/ml) in all samples. The concentrations of albendazole sulfoxide in plasma were extremely variable between individuals. In the first study of 10, the concentrations of albendazole sulfoxide in plasma are shown in Fig. 1. (In 2 of the volunteers only trace amounts (maximum 0.06 μg/ml) were found and these are omitted) and in the second study of 4 the median concentrations with and without oil/milk are shown in Fig. 2. After the same dose (400 mg) of albendazole, the maximum concentration varied from 0.04–0.55 μg/ml in the first study of 10 (Table 1) and from 0.19 to 1.14 μg/ml in the second group of 4 normal volunteers given albendazole (400 mg) without food. Similar concentrations of sulfoxide were found in patients being treated for their hydatid disease (Fig. 3) when allowance is made for differences in dosage regimen. Bile and hydatid

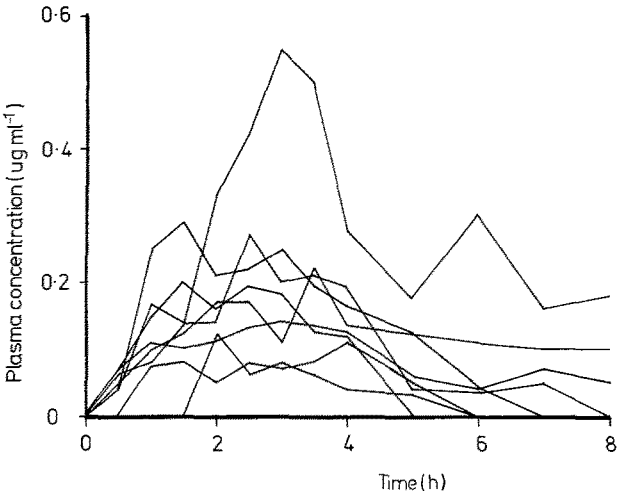

Fig. 1. The concentration of albendazole sulfoxide in plasma of 8 volunteers given albendazole orally as a single dose of 400 mg. (In 2 other volunteers the maximum concentration did not exceed 0.06 μg/ml at any time and are not shown)

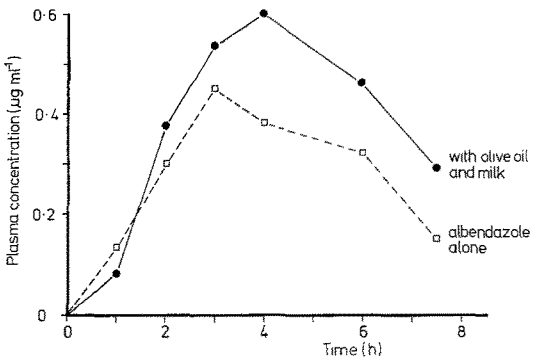

Fig. 2. The median concentrations of albendazole sulfoxide in plasma of 4 volunteers given albendazole (400 mg) as a single dose with and without olive oil/milk

Table 1. Pharmacokinetic parameters for albendazole sulfoxide in 10 volunteers after an oral dose of 400 mg of albendazole

	Mean ± SD	Range
C_{max} [μg ml^{-1}]	0.20 ± 0.15	0.04 ± 0.55
t_{max} [h]	2.35 ± 1.00	1–4
AUC [μg · h · ml^{-1}]	2.00 ± 2.77	0.42–8.95

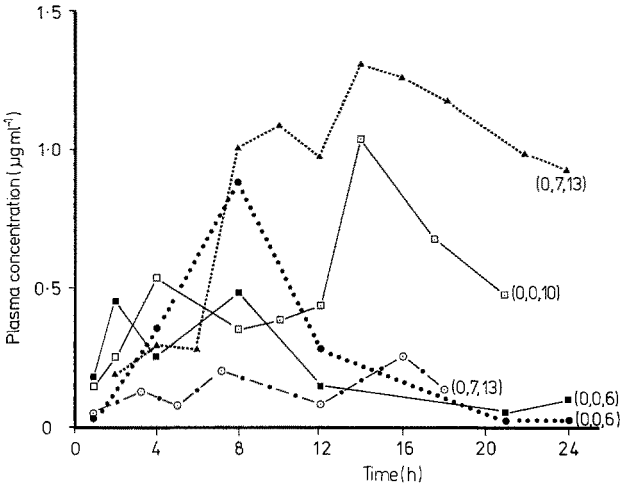

Fig. 3. The concentrations of albendazole sulfoxide in plasma of 5 patients infected with hydatid cysts and treated with albendazole (600 mg) given as three 200 mg tablets at times (h) shown (in brackets for each patient)

Table 2. Concentrations of albendazole sulfoxide (μg/ml) in bile, cyst fluid and plasma, taken simultaneously during surgical removal of hydatid cysts from 3 patients being treatment with approximately 10 mg/kg/day albendazole

Patient	Concentration of albendazole sulfoxide (μg/ml)			
	Plasma	Bile	Cyst	Day of albendazole treatment
C. E.	0.13	0		Day 1 (1 h)
	0.20	0		Day 1 (3 h)
	0.24	0.07	0.02	Day 1 (4 h)
	0.21	0.12	0.08	Day 1 (6 h)
C. H.	0.67		0.10	Day 5
M. O.	2.35		0.24	Day 28

Table 3. The areas under the plasma concentration/time (0-8 h) curve of albendazole sulfoxide in 4 volunteers after a single 400 mg dose of albendazole with and without olive oil/milk

Subject (Sex, age)	AUC with oil/milk	AUC without oil/milk	Ratio
IM (M, 22)	1.22	0.75	1.63
AW (M, 23)	3.26	3.88	0.84
JB (M, 43)	2.21	0.63	3.51
SM (F, 30)	6.82	5.84	1.17

cyst fluid concentrations were lower than those in plasma samples at the same times (Table 2).

T. L. C. analysis of urinary extracts (both unhydrolysed and acid hydrolysed) as described by Gyurik et al. [2] confirmed that in man as in other species the major urinary metabolite of albendazole is the sulfoxide. The renal clearances of sulfoxide in the 4 volunteers, IM, AW, JB and SM, given albendazole without food were 158, 436, 809, 541 $ml.h^{-1}$ respectively over the initial 8 h period and the cumulative urinary excretion of the sulfoxide over the initial 24 h period as a percentage of total dose was 0.09, 0.51, 0.14 and 0.88% respectively.

Discussion

Albendazole would appear to be metabolised extremely rapidly in man, as has been found in other species, such that at all times after administration of an oral dose of 400 mg of albendazole the concentrations in plasma were below the limit of detection (0.02 μg/ml) of the analytical technique. The metabolite found in plasma, the sulfoxide, is known to be anthelmintically active and it is probable that, at least outwith the gastro-intestinal tract, anthelmintic activity is due principally to the sulfoxide metabolite.

Plasma concentrations of albendazole sulfoxide found in hydatid patients were about 15-40 times higher than those of mebendazole obtained by Bryceson et al. [6] and Morris and Gould [7] in patients treated with mebendazole at a dose rate of 40-60 mg/kg, i.e. 4-6 times higher than the dose used in this study. Witassek et al. [8] reported maximum concentrations of about 0.10 μg/ml of mebendazole in patients on long term therapy at a dose rate of 16-48 mg/kg/day. Braithwaite et al. [9] reported mean maximum plasma concentrations of mebendazole after single oral doses of 10 mg/kg of 0.07 μg/ml (range 0.018-0.50 μg/ml; $n=12$). A single oral dose of 400 mg of albendazole in this study gave rise to a mean maximum concentration of 0.33 μg/ml (range 0.04-1.24 μg/ml; $n=8$) of albendazole sulfoxide. Braithwaite et al. [9] found much higher concentrations of 2 metabolites of mebendazole (the hydroxy metabolite and amino metabolite) in plasma. The hydroxy metabolite is said to have an anthelmintic potency of 10-50 times lower than that of mebendazole and the amino metabolite to have no anthelmintic activity (Thienpont, unpublished results; quoted by Meuldermans et al.) [10]. It is probable, therefore, that it is parent mebendazole concentrations which are important in the therapy of hydatid disease rather than those of the metabolites.

Cyst fluid concentrations of albendazole sulfoxide were considerably lower than those in plasma, but were higher than those obtained with mebendazole [7]. However, Luder et al. [11] in a detailed study of hydatid cyst concentrations of mebendazole showed that equilibrium between plasma and cyst fluid concentrations of mebendazole occurred slowly and that there was good agreement between the non protein bound concentrations in cyst and plasma, protein binding in cyst fluid varying greatly (0-95%) while binding in plasma was quite reproducible (~ 91%). Unfortunately in our study cyst

fluid protein binding was not measured. Albendazole sulfoxide plasma protein binding is about 70% (unpublished observation) and thus the cyst total concentrations found were similar or less than the unbound concentrations in plasma. Nevertheless, even with this limited data, it would appear that albendazole sulfoxide achieves higher concentrations in cyst fluid than those of mebendazole and may explain the more encouraging clinical response seen with albendazole in the treatment of hydatid disease [3].

The metabolic conversion of albendazole occurs rapidly in the liver of animals and probably this is the site of metabolism in man also. Sulfoxidation is known to be subject to genetic polymorphism [12] and this may also lead to the low plasma concentrations found in some individuals. Since albendazole per se is metabolised so rapidly as to be undetected in plasma in all subjects, it is likely that the variations in plasma concentrations between individuals are due to differences in absorption of albendazole rather than differences in metabolism. The pattern of urinary excretion also supported this view, subjects with highest plasma concentrations also having the highest urinary concentrations and highest total urinary excretion. Concentrations of albendazole sulfoxide in bile were low and this route of excretion would appear to be quantitatively of minor importance.

The poor absorption of albendazole and mebendazole in man is due to their poor aqueous solubility (<1 μg/ml in water at pH 7.4).

Munst et al. [4] report an eightfold increase in the concentration of mebendazole in plasma in a group of 3 volunteers when given with a fatty meal (ham and fried eggs), and Duncan and Watson [13] reported a 30% increase in mebendazole given in olive oil. The effect of fat (olive oil and milk) on absorption of albendazole is difficult to interpret. In one subject (JB) there was an approximate 3.5 times increase in absorption but in the other 3 subjects there was little change.

The concentrations of albendazole sulfoxide found in plasma of various animal species treated with albendazole are also found to be variable. However the clinical efficacy against all the major gastrointestinal helminth parasites of sheep and cattle is consistently high [14, 15]. Initial clinical studies of the efficacy of albendazole against the common gastro-intestinal helminths in man show good activity at the dose rate used in this study (400 mg) [16].

Acknowledgements. This study was supported in part by Smith Kline and French Laboratories Limited, Welwyn Garden City, Herts, U. K.

We are grateful to the clinicians who allowed and facilitated these studies on their patients.

References

1. Marriner SE, Bogan JA (1980) Pharmacokinetics of albendazole in sheep. Am J Vet Res 41: 1126–1129
2. Gyurik RJ, Chow AW, Zaber B, Brunner EL, Miller JA, Villani AJ, Petka LA, Parish RC (1981) Metabolism of albendazole in cattle, sheep, rats and mice. Drug Metab Dispos 9: 503–508
3. Morris DL, Dykes PW, Dickson B, Marriner SE, Bogan JA, Burrows FGO (1983) Albendazole in hydatid disease. Br Med J 286: 103–104
4. Munst GJ, Karlanganis G, Bircher J (1980) Plasma concentrations of mebendazole during treatment of Echinococcosis. Eur J Clin Pharmacol 17: 375–378
5. Bogan JA, Marriner SE (1980) Analysis of benzimidazoles in body fluids by high performance liquid chromatography J Pharm Sci 69: 422–423
6. Bryceson ADM, Woestenborghs R, Michiels M, Van Den Bossche H (1982) Bioavailability and tolerability of mebendazole in patients with inoperable hydatid disease. Trans R Soc Trop Med Hyg 76: 563–564
7. Morris DL, Gould SE (1982) Serum and cyst concentrations of mebendazole and flubendazole in hydatid disease. Br Med J 285: 175–179
8. Witassek F, Burkhardt B, Eckert J, Bircher J (1981) Chemotherapy of alveolar echinococcosis. Eur J Clin Pharmacol 20: 427–433
9. Braithwaite PA, Roberts MS, Allan RJ, Watson TR (1982) Clinical pharmacokinetics of high dose mebendazole in patients treated for cystic hydatid disease. Eur J Clin Pharmacol 22: 161–169
10. Meuldermans WEG, Hurkmans RMA, Lauwers WFJ, Heykants JJP (1976) The in vitro metabolism of mebendazole by pig, rat and dog liver fractions. Eur J Drug Metab Pharmacokinet 1: 35–40
11. Luder PJ, Witassek F, Weigand K, Eckert J, Bircher J (1985) Treatment of cystic echinococcosis *(Echinococcus granulosus)* with mebendazole. Assessment of bound and free drug levels in cyst fluid and of parasite vitality in operative specimens. Eur J Clin Pharmacol 28: 279–285
12. Waring RM, Mitchell SC, Shah RR, Idle JR, Smith RL (1982) Polymorphic sulphoxidation of S-carboxylmethyl-l-cysteine in man. Biochem Pharmacol 31: 3151–3154
13. Dawson M, Watson TR (1985) The effect of dose form on the bioavailability of mebendazole in man. Br J Clin Pharmacol 19: 87–90
14. Theodorides VJ, Nawalinski T, Chang J (1976) Efficacy of albendazole against gastrointestinal nematodes of cattle. Am J Vet Res 37: 1517–1518
15. Theodorides VJ, Nawalinski T, Chang J (1976) Efficacy of albendazole against *Haemonchus Nematodirus Dictyocaulus* and *Monezia* of sheep. Am J Vet Res 37: 1515–1516
16. Rossignol JF, Couland JP (1982) Proceedings of Symposium; Albendazole in Helminthiasis, Nairobi, June 1982. R Soc Med 57: 19–25

Received: April 6, 1984
accepted in revised form: April 18, 1986

Prof. J. A. Bogan
Department of Veterinary Pharmacology
University of Glasgow
Bearsden Road, Bearsden
Glasgow G61 1QH, UK