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Increased Systemic Availability of Albendazole when Taken with a Fatty Meal

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Summary. We have studied the systemic availability of oral albendazole in 6 patients with echinococcosis either fasting or with breakfast. Albendazole sulphoxide, the pharmacologically active principle, was assayed by HPLC.

Mean plasma concentrations and AUCs were 4.5 times higher when albendazole was given with breakfast than when administered in the fasting state.

We conclude that therapy of echinococcosis with albendazole requires the drug to be taken with meals and that administration on an empty stomach might be more appropriate when intraluminal effects are desired, e.g. for intestinal parasites.

Key words: albendazole, echinococcosis; bioavailability, food intake, fatty meal

It has been demonstrated that the outcome of therapy of hydatid disease with mebendazole depends on the plasma concentrations of the drug [1] and that these concentrations are markedly higher when the doses were given with a fatty meal [8]. To test whether or not the latter is also true for albendazole, an alternative benzimidazole compound active in echinococcosis [7], we have investigated the time course of the plasma concentrations of the active principle, albendazole sulphoxide, when albendazole was given to patients either fasting or together with a fatty breakfast.

Materials and Methods

Patients

Six patients (5 male, 1 female, age 31-56 years, body weight 57.5-99.0 kg, mean 70.8 kg) with hydatid disease (five with metacestodes of *Echinococcus granulosus*, and one with metacestodes of *Echinococcus multilocularis*) at the start of a course of albendazole therapy. Two patients had had prior anthelminthic therapy with mebendazole, which was stopped at least three weeks before the beginning of treatment with albendazole. All the patients gave their informed consent to take part.

Study Protocol

Two pharmacokinetic experiments were performed in each patient with an interval of 3 to 10 days, both after an overnight fast. On one day the patients took 400 mg albendazole together with 200 ml of water at 08.00 a.m. and fasted for 4 h. On the other day they took albendazole in the same dose in the middle of a breakfast consisting of eggs, butter, ham, bread, and coffee (estimated fat content 40 g). The sequence of the procedures was varied. On both days the patients had lunch 4 h after drug administration. Blood samples (8 ml) were taken before and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, and 8.0 h after dosing and were immediately centrifuged. The plasma was separated and stored at $-80\,^{\circ}C$ for less than ten weeks.

Analytical Procedures

To 1 ml of serum 20 µl of internal standard solution (SK&F 81380, 200 $\mu g \cdot ml^{-1}$) and 5 ml of ethyl acetate were added and mixed gently at room temperature on a horizontal shaker for 15 min. After centrifugation for 10 min at 2800 g 4 ml of the organic layer were transferred into a clean tube and evaporated to dryness under nitrogen. The residue was reconstituted in 100 µl of acetonitrile and aliquots of 10 µl were injected for chromatography.

An HPLC system of E. Merck/Hitachi (Darmstadt, FRG), consisting of a solvent delivery pump, a UV-detector, and a D2000 integrator was used. It

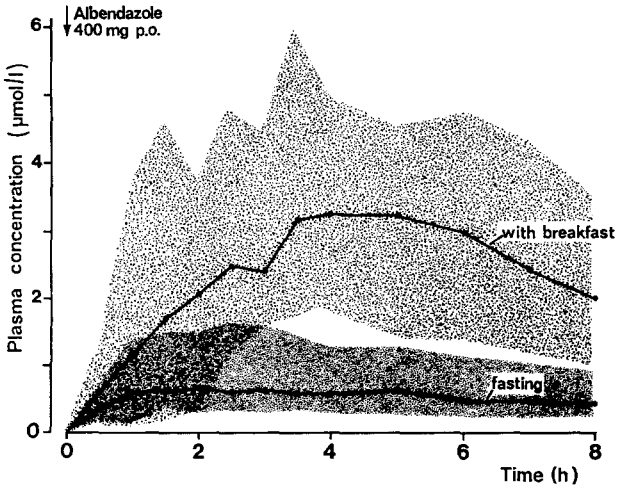

Fig. 1. Median plasma concentrations of albendazole sulphoxide. The *shaded areas* are the complete ranges

Table 1. Pharmacokinetics of albendazole (400 mg orally)

Patient	t_{max} (h)		C_{max}[a] ($\mu mol \cdot l^{-1}$)		AUC(0-8)[a] ($\mu mol \cdot l^{-1} \cdot h$)	
	fasting	with breakfast	fasting	with breakfast	fasting	with breakfast
1	2.0	3.5	0.45	1.75[b]	2.5	9.6[b]
2	3.0	3.5	0.85	2.20	4.3	11.3
3	0.5	3.5	0.40[b]	5.95[c]	2.0[b]	20.2
4	2.5	6.0	1.60[c]	5.25	8.6	21.2
5	3.0	4.0	1.55	5.00	9.0[c]	28.0
6	1.0	6.0	0.80	4.85	3.9	29.5[c]
Median:	2.25	3.75	0.83	4.93	4.1	20.6

[a] Albendazole sulphoxide concentration in plasma; [b] lowest value; [c] highest value

was equipped with a stainless steel column (20 × 4.5 mm I.D.) prepacked with 5 μm LiChroSorb Si-60 (E. Merck, Darmstadt). The solvent consisted of methanol, acetonitrile, and water (93:5:2, v:v:v). The flow rate was 2 $ml \cdot min^{-1}$. Detection was carried out at 290 nm with 0.0025 AUfs.

Calibration of the assay was performed every thirtieth sample with a 3.9 $\mu mol \cdot l^{-1}$ standard extracted in the same way as the samples. The assay was controlled with spiked plasma at two different control concentrations (0.2 and 1.9 $\mu mol \cdot l^{-1}$ respectively). The coefficients of variation ranged from 23% at 0.2 $\mu mol \cdot l^{-1}$ (detection limit) to 4.9% at 1.9 $\mu mol \cdot l^{-1}$ and 3.2% at 3.9 $\mu mol \cdot l^{-1}$. Albendazole sulphoxide concentrations in blank samples were below the limit of detection in all experiments.

Albendazole sulphoxide and the internal standard SK&F 81380 were gifts of Smith Kline and French (Göttingen, FRG). All other reagents were of LiChroSolv-quality (E. Merck, Darmstadt, FRG).

Calculations and Statistics

The AUC(0-8) was calculated by the linear trapezoidal method and statistical analyses by analysis of variance.

Results

Median plasma concentrations of albendazole sulphoxide were much higher when albendazole was taken with the meal than when given on an empty stomach (Fig. 1). Maximum plasma concentrations (C_{max}) ranged from 0.4 to 1.6 $\mu mol \cdot l^{-1}$ in fasting subjects and from 1.8 to 6.0 $\mu mol \cdot l^{-1}$ when albendazole was taken with the meal (Table 1). The latter C_{max} were 4.61 times higher on average (95% confidence intervals: 2.35 to 9.03) than the C_{max} when the drug was taken fasting ($F = 34$, $p < 0.001$). The corresponding AUC(0-8) were 19.9 ± 8.2 and 5.0 ± 3.0 $\mu mol \cdot l^{-1} \cdot h$ respectively. Based upon the AUC(0-8) of albendazole sulphoxide the systemic availability of albendazole taken with the meal was estimated to be 425% (95% confidence intervals: 230 to 787), relative to administration fasting ($F = 36$, $p < 0.001$). The inter-subject variability of these values was very large, the AUC(0-8) ranging from 2.0 to 9.0 in the fasting condition, and from 9.6 to 29.5 $\mu mol \cdot l^{-1} \cdot h$ when taken with a standard breakfast. Interestingly the values of AUC(0-8) measured in the two conditions were not correlated with each other. No patient reported any discomfort to albendazole, neither fasting nor when the drug was taken with the meal.

Discussion

The higher systemic availability of albendazole when taken with breakfast is compatible with previous studies. Münst et al. reported an eightfold increase in mebendazole plasma concentrations after a similar meal in three volunteers [8], whereas Dawson et al. found an increase in mebendazole plasma concentrations of only 30% after ingestion of the drug with olive oil [2]. For albendazole Marriner et al. demonstrated an inconsistent increase in plasma concentrations of albendazole sulphoxide in four volunteers who took albendazole with an oil/milk suspension. One of them had a 3.5 times increase in plasma concentrations, whereas there were only small changes in the other three subjects [6]. Presumably a full meal is more suitable for investigating the effects of food than an oil/milk suspension.

Our results appear to be in good agreement with clinical experience of mebendazole. Administration of the drug to fasting patients leads to low plasma concentrations and fatty adjuncts have only slight effects in increasing plasma concentrations, as demonstrated above. Only when the drug is administered during meals is a clinically relevant increase in plasma concentrations achieved [8].

An increased systemic availability of drugs taken with a meal cannot be expected a priori. As a result of slower gastric emptying and of chemical binding by components of the meal absorption of most compounds is delayed when they are taken with food. Only a few substances, e.g. griseofulvin, nitrofurantoin, and propoxyphene, exhibit higher systemic availability when taken with a meal [9]. The reasons for this are complex. On the one hand, it is assumed that in the duodenum neutral fat raises bile flow and resorption improves as a result of increased detergent action by bile acids. On the other hand, delayed gastric emptying leads to better dissolution of drugs within the gastric and intestinal contents. Another explanation for higher plasma concentrations after a drug is taken with a meal may be a reduction in first-pass elimination due to increased hepatic blood flow after meals [4]. However, the relative importance of these mechanisms to the increased systemic availability of albendazole remains speculative.

Our results may have several major practical consequences. When a systemic pharmacological effect of albendazole is required, e.g. in echinococcosis, maximal systemic availability is desirable and may be achieved by giving albendazole together with a fatty meal. However, in conditions where low systemic availability and a high intraluminal content of the drug is desirable, as in the treatment of intestinal helminthiasis [3], the drug should be taken on an empty stomach in order to reduce its absorption. Taking the drug 1 h before a meal might be suitable, but this should be investigated further.

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