EFFECT OF DOSE INCREASE OR CIMETIDINE CO-ADMINISTRATION ON ALBENDAZOLE BIOAVAILABILITY

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Abstract. The low bioavailability of albendazole affects the therapeutic response in patients with echinococcosis. Cimetidine co-administration is reported to improve bioavailability. To analyze the assumed dose-dependent bioavailability of albendazole, we administered 5 to 30 mg/kg albendazole to 6 male volunteers in a randomized cross-over study. To assess the effect of cimetidine (10 mg/kg twice daily), the drug was given with albendazole (20 mg/kg). A dose-dependent bioavailability was not observed. This was due to inter-individual variability of the maximal concentration (C_{max} 38%–72%) of albendazole sulphoxide (ABZSX), the active metabolite of albendazole. C_{max} was 0.21 ± 0.14 mg/L after 5 mg/kg and 0.39 ± 0.19 mg/L after 30 mg/kg albendazole ($P = 0.217$). Cimetidine tended to decrease C_{max} by 52% ($P = 0.109$) and significantly inhibited ABZSX breakdown as indicated by the prolongation of ABZSX elimination half-life from 7.4 ± 3.3 hr to 19.0 ± 11.7 hr ($P = 0.028$). Remarkably, the inter-individual variability of C_{max} was significantly lower during cimetidine co-administration: 14% versus 72%.

INTRODUCTION

Albendazole is a benzimidazole derivative used for treatment of intestinal helminthiasis and echinococcosis. Albendazole is an effective drug for treatment of these diseases but the therapeutic response in echinococcosis is poorly predictable due to the poor bioavailability.[1–4] After intestinal absorption, the drug is rapidly converted by the liver and probably also by mucosal cells into the active metabolite ABZSX, a mixture of R(+) and S(−) enantiomers. Formation of R(+)ABZSX is catalyzed by microsomal flavin monooxidase (FMO) and of S(−)ABZSX by cytochrome P450 enzymes (CYP3A). The extent to which both enzyme systems contribute to this process is variable from species to species and not well known in humans.[5,6] This so called first-pass effect of albendazole is almost 100%. Subsequently, ABZSX is converted by other cytochrome P450 enzymes (CYP2C) into the inactive metabolite albendazole sulfone.[7] In plasma, ABZSX is readily detectable by high-pressure liquid chromatography (HPLC). The parent compound and the inactive metabolite are present in very low concentrations.[8] It is not well known which ABZSX concentrations are reached at the usual and supratherapeutic albendazole doses and which concentrations are required for an appropriate therapeutic response. *In vitro* and *in vivo* studies demonstrated, however, that ABZSX concentrations in cyst fluid of 0.50 mg/L and higher were scolecidal and that long-term treatment improved outcome.[9–12]

Several pharmacokinetic studies have shown that combining albendazole with a fatty meal results in a 4- to 8-fold increase of ABZSX C_{max} and of the areas under the curve (AUC) of ABZSX concentration versus time.[13–15] In contrast, in one study no increase in C_{max} was demonstrated when albendazole was combined with a fatty meal.[16] The inter-individual variability in these studies was great. Therefore, it is unclear whether increasing the albendazole dose results in a linear increase of albendazole bioavailability, although a proportional increase of ABZSX concentration was reported after administration of a 50% greater dose of albendazole.[14]

Attention has recently been drawn to the beneficial effect of cimetidine co-administration with albendazole. Patients with echinococcosis treated with the combination of albendazole and cimetidine had fewer viable cysts and higher ABZSX concentrations in cyst fluid and bile than patients treated with albendazole alone. Serum ABZSX concentrations were not different.[17] The pharmacologic basis of this observation has not been elucidated but it is possible that inhibition of gastric acid secretion and mucosal and hepatic CYP enzymes by cimetidine plays a role. The overall effect of cimetidine co-administration on plasma ABZSX concentrations is not well defined. In the present report, we studied plasma ABZSX concentrations in relation to albendazole dose and the effect of cimetidine co-administration on ABZSX concentration.

MATERIALS AND METHODS

Study subjects. Six healthy male volunteers (age 19–21 years; weight 55–92 kg; body mass index 17–25 kg/m²) participated. Albendazole was administered with water on an empty stomach after an overnight fast. Food was withheld for 4 hours after the drug was taken but non-caffeine and non-alcoholic beverages were allowed. Subsequently, a light meal was offered and other dietary restrictions were removed. The light meal consisted of a cheese roll, 150 ml skimmed milk, and an apple (30 g fat, 49 g carbohydrates, 25 g protein, 575 kcal).

Albendazole (SmithKline Beecham) from one batch was provided by the hospital pharmacy as a powder in capsules and administered as a single oral dose: 5, 10, 20, or 30 mg/kg body weight. The actual albendazole doses were within 3% of calculated doses and were administered in a randomized order with at least a one-week wash-out period. In a separate study, albendazole (20 mg/kg) was combined with cimetidine (SmithKline Beecham, 10 mg/kg twice daily). Cimetidine was started 48 hours before the study and continued during the study.

Immediately before and 1, 2, 3, 4, 6, 8, 11, 24, and 36 hours after drug administration venous blood samples were taken from an indwelling catheter placed in the lower arm. Blood was collected into heparinized tubes, centrifuged im-
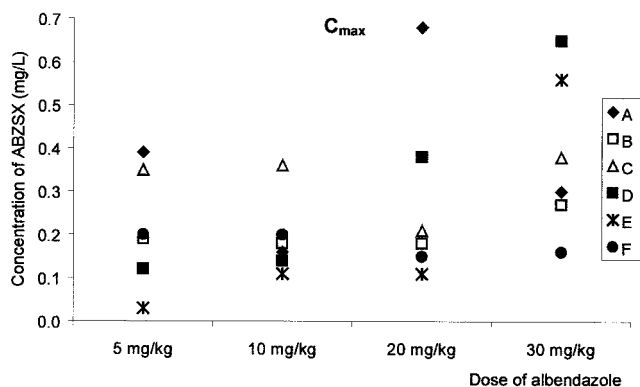
FIGURE 1. C_{max} of ABZSX in six healthy male subjects after administration of single oral doses of 5, 10, 20, or 30 mg/kg albendazole. Each subject is indicated by a different symbol.

mediately and plasma samples were stored at minus 70 °C until assayed.

Written informed consent was obtained from all volunteers. The study was approved by the Institutional Review Board of the Academic Medical Center, Amsterdam.

Albendazole sulfoxide assay. ABZSX concentrations were measured according to a modified method.[8] Briefly, plasma samples were slowly defrosted and centrifuged at 4,000 rpm for 10 minutes. Then, 400 μl of 3% perchloric acid was slowly added to 400 μl of plasma with the internal standard of hydroxy-mebendazole 0.02 g/L. After 30 minutes the denatured samples were centrifuged at 14,000 rpm for 10 minutes. The supernatant was subjected to HPLC using a Kipp Analytica 9209 HPLC autosampler (Jasco FP-920 UV-detector, Hewlett Packard 3390A integrator recorder) and a 100 × 4.6 3 μm CN spherisorb column. The wavelength was set at 293 nm, the flow rate was 1.0 ml/min, and the injection volume 100 μl. The mobile phase consisted of 100 mmol acetic acid buffer containing 15% methanol, pH 3.5. Quantitation of ABZSX was calculated by integration using the ratio of the peak height of ABZSX to the internal standard hydroxy-mebendazole. HPLC conditions used to measure ABZSX produced well-defined peaks, with retention times of 8 min for ABZSX and 11 min for the internal standard. A calibration curve was constructed by adding 3.0, 1.0, 0.5, 0.3, 0.1, 0.05, and 0.025 mg/L ABZSX plus 20 μl of the internal standard to plasma. The detection limit was 0.05 mg/L ABZSX and the calibration curve was linear between 0 and 1.5 mg/l (r = 0.999). The coefficients of variation of the within- and inter-day reproducibility were 5–10% depending on concentration.

Pharmacokinetics and statistics. C_{max} and T_{max} (the time to reach C_{max}) were read directly from the observations. Terminal phase elimination rate constants (k_{el}) for ABZSX were determined from the terminal five samples. The corresponding elimination half-lives were calculated as 0.693/ $k_{el.}$ AUC_{0-24} of plasma concentration versus time were calculated by the linear trapezoidal method. The Friedman test was used to compare pharmacokinetic parameters between more than two of paired observations and Wilcoxon ranks sum test between two groups of paired observations, using SPSS for Windows.[18]

Albendazole (mg/kg)	C_{max} (mg/L)	AUC_{0-24} (mg·h/L)
5	0.21 ± 0.14	1.92 ± 1.37
10	0.24 ± 0.09	2.08 ± 0.61
20	0.29 ± 0.21	2.72 ± 1.86
30	0.39 ± 0.19	3.68 ± 1.52
20 + cimetidine	0.14 ± 0.03	1.95 ± 0.35

RESULTS

The subjects did not encounter adverse events from the single, high doses of albendazole. ABZSX concentrations could be readily detected in the HPLC assay. The concentrations of the parent compound albendazole and the inactive metabolite albendazole sulphon were too low for quantitation. After administration of albendazole, a remarkable variability was observed among individual subjects at every dose given (Figure 1). The coefficient of variation for C_{max} varied from 38–72% and for AUC_{0-24} from 29–71%, independent of the albendazole dose (Table 1).

Intra-individual variability of ABZSX concentrations was also great and is illustrated in Figure 2 for subject A. The highest ABZSX concentrations were detected with a dose of 20 mg/kg albendazole. Administration of 30 mg/kg resulted in lower levels than 5 mg/kg and only slightly higher concentrations than 10 mg/kg. When data from all six subjects at the four different albendazole doses were compared as a group, the mean ABZSX concentration versus time curves overlapped with the lower albendazole doses (5 and 10 mg/kg), and there was a stepwise increase after administration of 20 and 30 mg/kg albendazole (Figure 3). The increase in mean C_{max} and AUC_{0-24} was neither linear nor significant due to the great intra- and inter-individual variability of albendazole concentrations (P values 0.217 and 0.221, respectively). The elimination half-lives following all four doses was 7.9 ± 3.6 hours and was not dose dependent (P = 0.261). T_{max} was reached 2.7 ± 0.8 hr after drug administration.
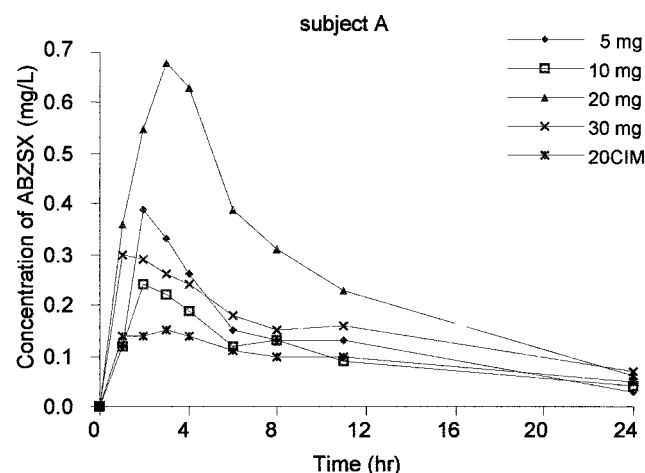

FIGURE 2. ABZSX concentration versus time curves in subject A after administration of single oral doses of 5, 10, 20, or 30 mg/kg albendazole.
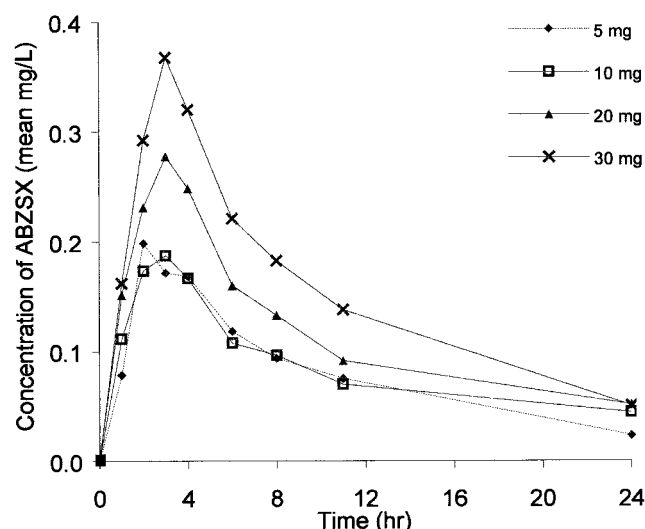
FIGURE 3. Mean ABZSX concentration versus time curves in six healthy male subjects after administration of single oral doses of 5, 10, 20, or 30 mg/kg albendazole.

Remarkably, inter-individual variability of C_{max} and AUC_{0-24} was significantly lower when cimetidine was co-administered. The coefficients of variation for C_{max} were 14% versus 72% and for AUC_{0-24} 18% versus 68%. Cimetidine reduced mean C_{max} by 52% without reaching significance ($P = 0.109$). Mean AUC_{0-24} did not change significantly during cimetidine co-administration ($P = 0.400$) because the 2.6-fold prolongation of the elimination half-life ($P = 0.028$) compensated for the lower ABZSX concentrations. No increase of the parent compound albendazole was observed during cimetidine co-administration.

DISCUSSION

Albendazole is an antihelminthic drug that mainly acts on intestinal parasites. It is poorly absorbed and reaches high intraluminal but low systemic concentrations.[19] Despite its poor absorption, albendazole is also used for the treatment of systemic parasitic infections like echinococcosis because alternative drugs are not available.[2–4]

In most pharmacokinetic studies designed to investigate how to increase the concentrations of the active metabolite ABZSX, intra-individual and inter-individual variability was high.[13–15] Our data show a similar pattern. Intra-individual variability cannot be estimated accurately in the current study but is illustrated by the course of C_{max} in the six subjects (Figure 2). The inter-individual variability of mean C_{max} at four different doses varied from 38%–72% and was not dose-dependent. Due to this variability, increasing the albendazole dose 6-fold did not result in a linear or significant increase in mean C_{max}. After administration of 5, 10 or 20 mg/kg albendazole mean C_{max} was almost identical. Only after 30 mg/kg albendazole did mean C_{max} increase but the difference between the lowest and the highest dose was not significant. For treatment of echinococcosis, the recommended dose of albendazole is usually 5 mg/kg whereas to our knowledge a dose of 30 mg/kg is never used.[4,20]

The mechanism underlying the high inter-individual var-

iability of ABZSX concentrations is not known. It may be hypothesized that gastric acidity plays a role. In the present study, albendazole was administered with water, without food, and after an overnight fast. In such a situation, gastric acid secretion is likely to vary among individuals. When this variability is minimized by inhibiting gastric acid secretion with cimetidine, two effects on ABZSX concentrations may be observed if absorption is pH dependent. It may decrease such as is the case with itraconazole[21] and there may be less inter-individual variability. We observed both impaired and less variable absorption. Cimetidine co-administration tended to decrease mean C_{max} by 52%, and inter-individual variability was low compared to albendazole alone (14% versus 72%). This observation suggests that the absorption of albendazole is indeed pH dependent, with better absorption at lower pH. Cimetidine may however exert additional actions that affect albendazole pharmacokinetics. Cimetidine inhibits the activity of hepatic CYP enzymes. It may be speculated that the CYP-mediated metabolic conversion of albendazole into the S($-$) enantiomer is inhibited and thus making the FMO-mediated pathway a rate limiting factor for R($+$) enantiomer formation. This may result in lower ABZSX concentrations. However, this mechanism of action is tentative and needs further study. A better defined effect of cimetidine is the increase of concentrations of drugs that are metabolized by these CYP enzymes, such as mebendazole.[22] Therefore, the metabolism of ABZSX, which is also CYP dependent, may be inhibited by cimetidine co-administration and thereby increase the elimination half-life of ABZSX. In our study, a 2.6-fold prolongation of ABZSX elimination half-life was indeed observed after cimetidine co-administration. (7.4 $\pm$ 3.3 versus 19.0 $\pm$ 11.7 hours, respectively. $P = 0.028$). Another factor that deserves further study is the possible metabolism of albendazole by CYP enzymes in the intestinal mucosa. Inter-individual variability in mucosal CYP enzyme activity is great and may thereby contribute to variability of ABZSX concentrations.[23]

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