

Time Dependent Pharmacokinetics of Albendazole in Human

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ABSTRACT: The pharmacokinetics of the main metabolites of albendazole (albendazole sulphoxide (ABZ-SO) and albendazole sulphone (ABZ-SO₂)) were studied in 12 healthy human volunteers in a double blind design on the first and last days of oral administration of 800 mg albendazole daily for 15 days.

No significant differences were observed in C_{\max} , T_{\max} and V_d/F of ABZ-SO, whereas the AUC, AUMC and $T_{1/2}$ of this metabolite were significantly reduced and Cl/F was significantly increased in multiple dosing. There were also no significant differences in the C_{\max} , T_{\max} , V_d/F and $T_{1/2}$ of ABZ-SO₂, whereas the AUC and AUMC of this metabolite were significantly reduced and Cl/F was significantly increased in multiple dosing.

These observations suggest time dependent pharmacokinetics of albendazole (observed for ABZ-SO and ABZ-SO₂), which was explained on the basis of the induction of enzymes involved in the metabolism of ABZ-SO (albendazole sulphoxide) to metabolites other than albendazole sulphone in multiple dosing. Copyright © 2003 John Wiley & Sons, Ltd.

Key words: albendazole; albendazole sulphoxide; albendazole sulphone; time dependency; pharmacokinetics; metabolism

Introduction

Albendazole (ABZ) is a benzimidazole carbamate used as the drug of choice in the treatment of echinococcosis [1]. Few studies exist on the disposition, pharmacokinetics, and concentration-effect relationship of ABZ and its metabolites in the human. After oral administration, it is quickly oxidized into its pharmacologically active metabolite albendazole sulphoxide (ABZ-SO) [2]. Further liver oxidative metabolism produces albendazole sulphone (ABZ-SO₂), which is thought to be anthelmintically inactive.

The parent compound is undetectable in the serum after administration to man [3,4], rats [5], sheep [2], cattle [6] and other species. There are various controversial reports on induction or inhibition of microsomal enzyme function by ABZ or its metabolites [7–10], which may indicate nonlinearity in the pharmacokinetics of this drug. In rats, enhanced sulphonation of the sulphoxide metabolite has been observed after multiple dose treatment with the parent compound, which suggests autoinduction [9,10]. In human hepatoma cells ABZ-SO and ABZ-SO₂ induced CYP1A2 and UDP-GT, whereas the parent compound is claimed to inhibit the activity of these enzymes. Steiger *et al.* [8] observed that ABZ-SO concentration is decreased in the steady state compared with the first dose in hydatid patients treated with ABZ. They attributed this decrease to auto-induced metabo-

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lism [8]. This paper reports the further study of this phenomenon.

Materials and Methods

Drug administration and blood sampling

Twelve healthy human volunteers (4 women and 8 men), aged 21–44 years and weighing 51–77 kg were selected, from whom informed written consents were obtained. The study protocol and the consent forms were approved by the local review board. A complete medical history and physical examination, urinalysis and haematology tests were obtained for all volunteers prior to the initiation of the study. The volunteers were instructed to abstain from taking any medication for 1 week prior to and during the study period. The drug was administered orally to the overnight fasting subjects with 250 ml of water. The participants were given two standard commercial tablets of ABZ 400 mg each day for 15 days. Blood samples (10 ml) on the first and the last day were drawn at 0, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 12 and 24 h post dosing via an indwelling heparin-lock canula in the forearm vein. The samples collected in uncoated plain glass tubes were centrifuged for 10 min at 3000 rpm and sera were then separated and kept frozen at -20°C until assayed. Serum samples were analysed according to the method described by Mirfazaelian *et al.* [11].

Pharmacokinetic analysis

Pharmacokinetic parameters were obtained by noncompartmental analysis. The biological half-life ($T_{1/2}$) was calculated by the following relationship:

$$T_{1/2} = \ln(2)/k$$

where k is the terminal rate constant calculated from the slope of the terminal points. The last n points, regression-coefficient (r^2) of which there were more than 0.9 were considered as terminal points ($n \geq 4$).

The area under the concentration-time curve (AUC) was calculated by the trapezoidal rule to 24 h and then extrapolated to infinity using the terminal rate constant value [12]. The area under

the first moment curve AUMC_{0-24} was calculated through the following relationship:

$$\text{AUMC}_{t_1-t_n} = [(t_2 - t_1)(C_1t_1 + C_2t_2)/2] + \dots + [(t_n - t_{n-1})(C_{n-1}t_{n-1} + C_nt_n)/2]$$

the apparent oral clearance (Cl_p/F) of the two metabolites was calculated by the division of dose of the main drug to $\text{AUC}_{0-\infty}$ for each metabolite. Apparent distribution volume (V_d/F) resulted by dividing the apparent oral clearance (Cl_p/F) to the terminal rate constant (k). F was defined as the fraction of the dose transformed to each metabolite after absorption and reaching the general circulation; F of ABZ-SO (F_1) was defined as the fraction of the dose of the parent drug absorbed (F_a) and then turned to active metabolite (F_{m1}) (i.e. $F_1 = F_a \times F_{m1}$) and F of ABZ-SO₂ (F_2) was defined as fraction of dose of the parent drug absorbed (F_a) and then turned to active metabolite (F_{m1}) and thereafter metabolized to ABZ-SO₂ (F_{m2}) (i.e. $F_2 = F_a \times F_{m1} \times F_{m2} = F_1 \times F_{m2}$).

The above parameters were calculated for the last dose (15th day) after calculation of the residual concentrations and thereby the residual profile of each subject by the following relationship:

$$C[t_i\text{-residual}] = C[t_i\text{-observed}] - C[t_0]e^{-kt_i}$$

where k is the elimination rate constant of the last day and t_0 is defined as the administration time. The residual concentration at each time after the 15th dose administration ($C[t_i\text{-residual}]$) is the difference result of the observed serum concentration of that time ($C[t_i\text{-observed}]$) and the residual concentration of the 14th dose at the same time ($C[t_0]e^{-kt_i}$).

The derived parameters were subjected to paired t -test to evaluate the significance of the difference [13]. A p -value of less than 0.05 was considered significant.

Results

The serum concentration-time profiles of the ABZ main metabolites, ABZ-SO and ABZ-SO₂, on the first and last day of the study are shown in Figures 1 and 2, respectively. Table 1 illustrates

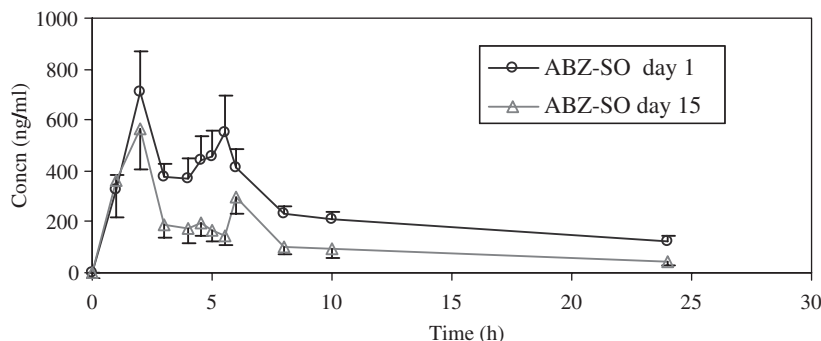


Figure 1. Mean serum profiles of albendazole sulphoxide (ABZ-SO) in volunteers taking oral daily doses (800 mg tablets) on the first and last day of drug administration (mean \pm SE)

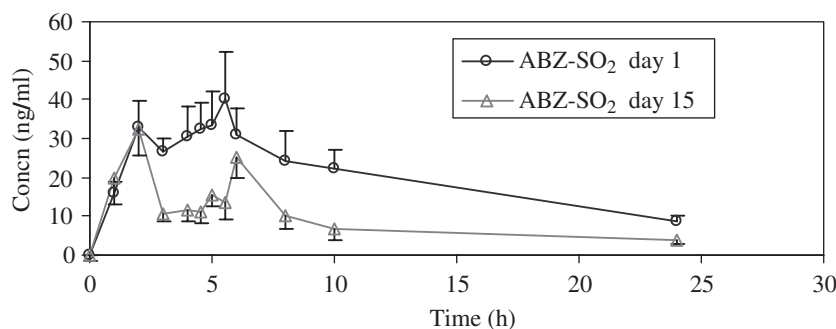


Figure 2. Serum profiles of albendazole sulphone (ABZ-SO₂) in volunteers taking oral daily doses (800 mg tablets) on the first and last day of drug administration (mean \pm SE)

Table 1. Demographics of the volunteers participating in the study

Subject	Sex (M/F)	Age (years)	Weight (kg)
1	F	33	53
2	F	34	51
3	F	22	66
4	F	25	73
5	M	44	68
6	M	39	77
7	M	27	73
8	M	21	77
9	M	23	69
10	M	31	70
11	M	22	76
12	M	34	59
Mean		29.58	67.67
SD		7.44	8.94

the demographics of the subjects participating in the study. Table 2 summarizes the pharmacokinetic parameters of ABZ-SO and ABZ-SO₂.

No significant differences were observed in the C_{\max} , T_{\max} and V_d/F of ABZ-SO, whereas the AUC, AUMC and $T_{1/2}$ of this metabolite were significantly reduced and Cl/F was significantly increased in multiple dosing.

No significant differences were observed in C_{\max} , T_{\max} , V_d/F and $T_{1/2}$ of ABZ-SO₂, whereas the AUC and AUMC of this metabolite were significantly reduced and Cl/F was significantly increased in multiple dosing.

Discussion

The pharmacokinetic profile of the two main metabolites of ABZ (ABZ-SO and ABZ-SO₂) were studied in single and repeated oral doses to investigate the possibility of induction or inhibition of microsomal enzymes by the main drug or its metabolites.

Table 2. Pharmacokinetic parameters of albendazole sulphoxide (ABZ-SO) and albendazole sulphone (ABZ-SO₂) on days 1 and 15 of administration in volunteers taking ABZ tablets (800 mg/day). mean \pm SD

Parameter ^a	ABZ-SO			ABZ-SO ₂		
	Day 1	Day 15	<i>t</i> -test	Day 1	Day 15	<i>t</i> -test
AUC _{0–24} (ng.h/ml)	5637.72 \pm 3490.67	3713.96 \pm 2205.31	0.02	469.03 \pm 350.73	284.55 \pm 170.72	0.04
AUMC _{0–24} (ng.h ² /ml)	34426.82 \pm 21024.09	19442.46 \pm 18576.34	0.04	3301.66 \pm 2495.05	1796.85 \pm 1363.70	0.04
<i>T</i> _{1/2} (h)	23.05 \pm 19.57	11.43 \pm 4.85	0.04	13.41 \pm 6.66	11.91 \pm 4.76	N.S.
<i>C</i> _{max} (ng/ml)	746.08 \pm 532.32	707.37 \pm 548.47	N.S.	62.69 \pm 73.35	39.61 \pm 21.33	N.S.
<i>T</i> _{max} (h)	3.35 \pm 1.75	2.77 \pm 1.74	N.S.	4.81 \pm 2.72	4.27 \pm 2.76	N.S.
<i>Cl/F</i> (l/h)	0.09 \pm 0.12	0.24 \pm 0.15	0.001	1.73 \pm 0.82	3.16 \pm 2.45	0.04
<i>V</i> _d / <i>F</i> (l)	2.34 \pm 2.87	3.84 \pm 3.29	N.S.	34.76 \pm 25.52	43.08 \pm 30.93	N.S.

^a Day 15 day parameters are calculated using residual serum concentrations.

The values obtained for the pharmacokinetic parameters of ABZ metabolites in the single dose were in good general agreement with earlier studies [6,14,15].

It is to be noted that this pharmacokinetic parameters of the last dose were calculated based on residual concentrations of each metabolite at steady state. Two separate sections (ABZ-SO pharmacokinetics and ABZ-SO₂ pharmacokinetics) discuss the results.

ABZ-SO pharmacokinetics

Evaluation of the pharmacokinetic parameters of ABZ-SO showed a reduction of the AUC and AUMC and an increase of *Cl/F*₁ on the last day of ABZ dosing in comparison with the first dose, instead of the expected no change in these parameters in linear pharmacokinetics. For example, the mean AUC and AUMC of ABZ-SO showed 34% and 44% decreases, respectively on the 15th dose compared with the 1st dose. The mean *Cl/F*₁ (*Cl/F* of ABZ-SO) showed a 96% increase on the 15th dose compared with the 1st dose.

These findings indicate that the pharmacokinetics of ABZ-SO is dependent on the duration of the administration of ABZ.

The significant decrease noted in the AUC of ABZ-SO with time in our subjects (about 34%) can be attributed to either (a) a decreased formation and/or (b) an increased elimination rate of this metabolite. As noted earlier, ABZ is quickly and almost completely transformed to its main metabolite (ABZ-SO) in the first pass metabolism and there are no reports on detection

of the main drug in biological fluids after oral administration of ABZ to human and animals [2,5–8,14]. Therefore the suggestion of decreased ABZ-SO formation is unlikely. Thereby this observation was attributed to an increased elimination rate of this metabolite with time. This can be as a result of autoinduction of the hepatic enzymes involved in further metabolism of ABZ-SO. This suggestion was further confirmed by the increased *Cl/F*₁ and decreased biological half-life (*t*_{1/2}) of ABZ-SO on the last day (in comparison with the first day). This was also in concordance with previous animal and human studies; in rats a reduced ABZ-SO concentration resulting from enhanced sulphonation of the sulphoxide metabolite (ABZ-SO) after multiple dose administration of ABZ was reported, which was indicative of autoinduction [9,10]. Also in a human study by Steiger *et al.* [8], the metabolite concentration dropped significantly in the second cycle of drug administration compared with the first one, which was attributed to enzyme induction. However, as they used single sample monitoring for each dose and an average of the two weekly cycles were then compared, interpretation of their results was rather obscure.

High inter-subject variation in our subjects was observed which is in concordance with previous studies [5,6,14–18]. Inter-subject variations can be attributed to the low *F* (about 1%) in humans [19] as a result of slow and erratic *in vivo* dissolution [16].

A lack of significant difference in the *C*_{max} and *V*_d/*F* of ABZ-SO on the first and last day of dosing was attributed to inter-subject variations,

though apparently increased on the last dose compared with the first.

ABZ-SO₂ pharmacokinetics

The evaluation of pharmacokinetic parameters of ABZ-SO₂ showed a reduction of the AUC and AUMC and an increase of Cl/F_2 on the last day of ABZ dosing in comparison with the first dose in a statistically significant level, instead of the expected no change in these parameters in linear pharmacokinetics. The mean AUC and AUMC of ABZ-SO₂ showed 39% and 46% decreases, respectively, on the 15th dose compared with the 1st dose. The mean Cl/F_2 (Cl/F of ABZ-SO₂) showed an 83% increase on the 15th dose compared with the 1st dose.

These findings indicate that the pharmacokinetics of ABZ-SO₂ is dependent on the duration of administration of ABZ.

A significant decrease was noted in the AUC of ABZ-SO₂ with time in our subjects (about 39%). This was in contrast with animal studies performed previously, as the AUC of ABZ-SO₂ was increased in multiple dosing in the rat [10]. It can be inferred that the relative contribution of metabolizing systems involved in ABZ-SO and ABZ-SO₂ in humans is different from those of the rat. This can be confirmed by the observation that the ratio of AUC of ABZ-SO₂ to that of ABZ-SO (ABZ-SO₂/ABZ-SO) in humans (less than 10% in our study) is far less than other animals (e.g. about 40% in sheep [20], 60% in goat [21], 70% in chicken [22], 80% in pig [23] and 90% in buffalo [24]). This could be related to the presence of other metabolic pathways involved in the further metabolism of ABZ-SO in humans. In other words, although ABZ-SO₂ is a major metabolite of ABZ-SO both in humans and animals, it consists of a relatively small fraction of its metabolites in man compared with other species.

The decreased AUC of ABZ-SO₂ with time may be the result of (a) a decrease in ABZ-SO₂ formation rate and/or (b): an increase in the ABZ-SO₂ elimination rate. As noted previously the ABZ-SO elimination rate is increased and thereafter increased formation of its metabolites should be expected. However, as noted in Table 2, the $t_{1/2}$ of ABZ-SO₂ in the two doses

were not significantly different. Therefore it is less likely that the ABZ-SO₂ elimination rate is increased with time (suggestion (b)). On the other hand, as noted above, ABZ-SO₂ does not consist of a high fraction of ABZ-SO metabolite, and in this instance for the AUC of ABZ-SO₂ to be decline with time, some other metabolic pathways of ABZ-SO metabolism might be activated, so that despite there being no change in the elimination rate of the metabolite at different time intervals, a diminished AUC is observed as a result of a decreased ABZ-SO₂ formation rate in humans (suggestion (a)).

Though there was an apparently increase on the last dose compared with the first one, the lack of significant difference in the C_{max} and V_d/F of ABZ-SO₂ on the first and last day of dosing was attributed to inter-subject variations.

Conclusions

The pharmacokinetics of the two main metabolites of ABZ (ABZ-SO and ABZ-SO₂) was investigated in humans following the administration of repeated oral doses (800 mg/day) in a double blind design between the first and last dose in a 15-day period.

No significant differences were observed in the C_{max} , T_{max} and V_d/F_1 of ABZ-SO, whereas the AUC, AUMC and $T_{1/2}$ of this metabolite, were significantly reduced and Cl/F was significantly increased in multiple dosing.

There were also no significant differences in the C_{max} , T_{max} , V_d/F_2 and $T_{1/2}$ of ABZ-SO₂, whereas the AUC and AUMC of this metabolite were significantly reduced and Cl/F was significantly increased in multiple dosing.

It was suggested that the above findings in pharmacokinetics of both ABZ-SO and ABZ-SO₂ are time dependent, which can be attributed to enzyme induction in metabolic pathways involving further metabolism of ABZ-SO to other metabolites (instead of ABZ-SO₂).

As ABZ-SO is the active metabolite of ABZ, and a lower blood concentration during time might cause significant effects on the pharmacotherapy of echinococcosis and cysticercosis, the clinical outcome is to be studied further.

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