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SHORT COMMUNICATION

Dose Dependent Pharmacokinetics of Albendazole in Human

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ABSTRACT: Pharmacokinetics of albendazole sulphoxide (ABZ-SO) in three different single oral doses of albendazole (ABZ) (400, 800 and 1200 mg) was studied in 10 healthy human volunteers in a double blind three-way crossover design. The serum levels of albendazole main metabolite, albendazole sulphoxide (ABZ-SO), were analysed by a modified high-pressure liquid chromatography method. (ABZ is not detectable in biological fluids itself.)

For ABZ-SO, there was no significant difference in the biological half life, normalized serum peak concentration ($C_{max-ABZ-SO}/Dose_{ABZ}$), time to reach peak concentration (T_{max}) and mean residence time (MRT), whereas apparent clearance (Cl_p/F), apparent distribution volume (V_d/F), normalized area under the serum concentration-time curve ($AUC_{ABZ-SO}/Dose_{ABZ}$) and normalized area under the first moment curve ($AUMC_{ABZ-SO}/Dose_{ABZ}$) of albendazole main metabolite (ABZ-SO) were statistically different at different doses of the parent drug, resulting in substantially lower serum concentration and thereafter $AUC_{ABZ-SO}/Dose_{ABZ}$ and $AUMC_{ABZ-SO}/Dose_{ABZ}$ in higher doses. These observations indicate dose dependent pharmacokinetics of albendazole (observed for ABZ-SO), which were explained on the basis of a change in fraction of dose absorbed (F) as a result of slow and incomplete dissolution of the main drug in the GI tract. Copyright © 2002 John Wiley & Sons, Ltd.

Key words: albendazole; albendazole sulphoxide; dose-dependency; pharmacokinetics; metabolism

Introduction

Albendazole (ABZ) is a benzimidazole carbamate used as the drug of choice in the treatment of echinococcosis [1]. After oral administration, it is quickly oxidized by both FMO and CYP, principally CYP3A4, into its pharmacologically active main metabolite, albendazole sulphoxide (ABZ-SO) enantiomers; ABZ-SO(+) and ABZ-SO(−), respectively [2,3]. Further liver oxidative and hydrolytic metabolism produces albendazole sulphone ($ABZ\text{-}SO_2$) and albendazole amino sulphone ($ABZ\text{-}SO_2\text{–}NH_2$), respectively, which are thought to be anthelmintically inactive. While ABZ possesses a clear therapeutic effect, some pharmacokinetic studies indicate that ABZ-SO is responsible for both anthelmintic and toxic effects [4,5].

Few studies exist on the disposition, pharmacokinetics and concentration-effect relationship of ABZ and its metabolites in human. The parent compound is undetectable in the serum after administration to man [6,7], rats [8], sheep [2], cattle [9] and other species. Though various dosing schedules are designed for the treatment of echinococcosis in human [10–13], there is only one report on the pharmacokinetics of ABZ-SO at different dose levels [14]. They observed no statistically significant difference in the C_{max}

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and AUC of ABZ-SO, which were apparently increased after single dose administration of various increasing doses of ABZ in 6 human subjects. They attributed their observation to great intra-individual and inter-individual variations. We intended to further study dependency of pharmacokinetic parameters of ABZ-SO and to dose in various oral single doses (400, 800, and 1200 mg) of ABZ.

Materials and Methods

Chemicals

Standard commercial oral dosage forms of ABZ were used. ABZ-SO reference standard was donated by SmithKline Beecham (Worthing, UK). ABZ and Mebendazole (MBZ) reference standards were gifted by Daroupakhsh Pharmaceutical Co., Iran. Methanol (HPLC grade, Merck) acetonitrile (HPLC grade, Merck) and glacial acetic acid (analytical grade, Merck) were used for high-pressure liquid chromatography analysis.

Drug administration, sampling and analysis

Ten healthy human volunteers (4 women and 6 men), aged 21–44 years and weighing between 51–77 kg were selected. A complete medical history, physical and laboratory examination were obtained for all volunteers prior to the initiation of the study. The study was approved by the local ethics committee and was carried out in biopharmaceutics laboratory of Faculty of Pharmacy, Tehran University of Medical Sciences. Subjects showing abnormal liver function, blood pressure and respiratory function were excluded from 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 in fasting state with 250 ml of water. The participants were given one, two or three tablets of ABZ 400 mg in a randomized double blind three-way crossover design with a washout period of one week between the treatments. Blood samples (10 ml) were drawn at 0, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 12 and 24 h post-dosing via an indwelling canula in the forearm vein. The samples were then centrifuged for 10 min at 3000 rpm and sera were separated and kept frozen at -20°C until assayed.

Serum samples were extracted and analysed according to the methods described by Zeugin *et al*. [15] (1990) and Mirfazaelian *et al*. [16] (2000), respectively, with few modifications.

Pharmacokinetic analysis

Pharmacokinetic parameters were obtained by non-compartmental analysis. Apparent first order terminal rate constant (k) was calculated from the terminal portion of the plasma concentration-time curve using least square regression analysis of the logarithm of concentration versus time. Biological half-life ($T_{1/2}$) was calculated by the following relationship:

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

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 [17]. Area under the first moment curve ($AUMC_{0-24}$), $AUMC_{0-\infty}$ and mean residence time (MRT) were calculated through the following relationships:

$$AUMC_{t1-tn} = [(t_2 - t_1)(C_1 t_1 + C_2 t_2)/2] + \cdots + [(t_n - t_{n-1})(C_{n-1} t_{n-1} + C_n t_n)/2]$$

$$AUMC_{tn-\infty} = C_n t/k + C_n/k^2$$

$$AUMC_{t1-\infty} = AUMC_{t1-tn} + AUMC_{tn-\infty}$$

$$MRT = AUMC_{0-\infty}/AUC_{0-\infty}$$

Apparent oral clearance (Cl_p/F) of ABZ-SO was calculated by division of the dose of the main drug to $AUC_{0-\infty}$ of the metabolite. Apparent distribution volume (V_d/F) was resulted by dividing apparent oral clearance (Cl_p/F) to the terminal rate constant (k). F was defined as the fraction of the dose of the main drug transformed to metabolite and reached to the general circulation. As the first pass metabolism of the main drug to ABZ-SO is reported to be about 100% [14], the calculated F value would approximately be equal to the fraction of the dose absorbed.

Serum concentration (C_{max}), area under serum concentration–time curve (AUC) and area under

the first moment curve (AUMC) of ABZ-SO at different doses were normalized by division of the values to their relative ABZ doses and the derived parameters are shown as C^*_{max}, AUC* and AUMC*, respectively, hereafter. The derived parameters were subjected to repeated measures two-way ANOVA to evaluate the significance of the difference [18]. For further assessment of the difference they were then tested by Tukey–Kramer multiple comparisons post hoc test. *P*-value of less than 0.05 was considered significant.

Results

No significant adverse reaction was noted in the subjects in terms of both clinical and laboratory tests (ALT, AST) in the dose range studied. Serum concentration-time profiles of ABZ main metabolite, ABZ-SO, at three ABZ dose levels studied are shown in Figure 1. Table 1 summarizes pharmacokinetic parameters of ABZ-SO at ABZ dose range studied.

No significant differences were observed in the $t_{1/2}$, C^*_{max}, T_{max} and MRT of ABZ-SO, whereas AUC* and AUMC* were significantly reduced and Cl_p/F and V_d/F were significantly increased with increasing administered ABZ dose.

Discussion

The values of the pharmacokinetic parameters of ABZ-SO were in good general agreement with earlier studies [19,20].

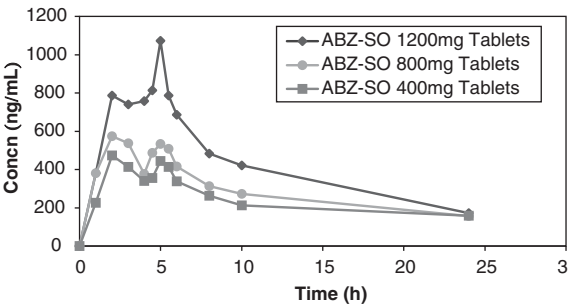

Figure 1. Mean serum profiles of albendazole sulphoxide (ABZ-SO) in volunteers taking different single oral doses of ABZ (400, 800 and 1200 mg tablets)

Statistical evaluation of pharmacokinetic parameters of ABZ-SO showed reduction of AUC* and AUMC* and increase of Cl_p/F and V_d/F with increasing ABZ dose instead of the expected no change in these parameters in linear pharmacokinetics. For example, mean AUC* of ABZ-SO showed 50.40% decrease when ABZ dose was doubled from 400 to 800 mg and 53.63% decrease when it was tripled from 400 to 1200 mg.

These findings indicate that the pharmacokinetics of ABZ-SO is dependent on the administered dose of the main drug.

Schipper *et al.* [14] studied pharmacokinetics of ABZ-SO after single dose administration of 5, 10 and 20 mg/kg – which is approximately equal to 400, 800 and 1600 mg ABZ/subject. They reported no significant change in the *non-normalized* C_{max} and $AUC_{0–24}$ of ABZ-SO in their subjects (6 volunteers) instead of the expected significant change in the *non-normalized* parameters in linear pharmacokinetics. They attributed their observations to great intra-individual and inter-individual variations. We also observed high variations between our subjects, which is in concordance with previous studies [6,7,14, 19,21,22]. Inter-subject variations can be attributed to the low *F* (about 1%) in humans [23]. But as significant increase was noted in Cl_p/F and V_d/F with increasing ABZ dose in our subjects, another reason can be proposed for this observation (instead of inter-subject variation suggested by Schipper *et al.* [14]); Increase in Cl_p/F and V_d/F with increasing dose of the main drug can be as a result of either increase in clearance (Cl_p) and distribution volume (V_d) or decrease in the fraction of dose of the main drug transformed to the metabolite and reached to the general circulation (*F*). The increase in Cl_p is normally along with decreased $t_{1/2}$ or increased V_d. As noted above, biological half life of ABZ-SO remained unaffected by increasing dose of the main drug. There is also a moderate protein binding reported for this metabolite in the literature (63–65%) [24], which lessens the possibility of saturation of plasma proteins and therefore change in V_d in the ABZ dose range studied. Though possibility of simultaneous offsetting change in V_d and Cl_p cannot be ruled out (No change in *F*), increased Cl_p/F and V_d/F can most likely be resulted by decrease in the fraction of

Table 1. Pharmacokinetic parameters of albendazole sulphoxide (ABZ-SO) in volunteers taking different single oral doses of ABZ (400, 800 and 1200 mg Tablets) Mean ± SD

Parameter	ABZ Dose			ANOVA
	400 mg	800 mg	1200 mg	
AUC^*_{0-24} ($h.m^{-3}$)	17.74 ± 11.70	8.80 ± 4.34	8.51 ± 6.77	0.007
$AUMC^*_{0-24}$ ($h^2.m^{-3}$)	175.25 ± 114.68	80.93 ± 32.74	73.90 ± 54.72	0.043
MRT (h)	25.56 ± 9.46	21.36 ± 8.33	17.00 ± 6.03	N.S.
$T_{1/2}$ (h)	17.63 ± 7.48	13.94 ± 5.83	11.54 ± 4.87	N.S.
C^*_{max} (m^{-3})	1.61 ± 0.93	1.21 ± 0.28	1.12 ± 1.41	N.S.
T_{max} (h)	3.06 ± 1.33	3.3 ± 0.19	3.65 ± 1.61	N.S.
Cl_p/F ($m^3.h^{-1}$)	0.04 ± 0.02	0.09 ± 0.03	0.14 ± 0.09	0.001
V_d/F (m^3)	1.05 ± 0.56	1.73 ± 0.79	2.08 ± 1.19	0.012

AUC^*: Area under the curve of metabolite normalized to dose of the main drug.
$AUMC^*$: Area under the first moment curve of metabolite normalized to dose of the main drug.
C^*_{max}: Peak serum concentration of metabolite normalized to dose of the main drug.
N.S.: Non-significant ($p > 0.05$).

the main drug metabolized and reached to the general circulation (F). Decrease in F can itself be either as a result of (a) saturable sulphoxidation, (b) saturable absorption of ABZ-SO from GI or (c) poorer dissolution in higher doses of the main drug. As noted earlier ABZ is quickly and completely transformed to its main metabolite (ABZ-SO) by hepatic first pass metabolism, which indicate existence of high capacity enzymes responsible for this conversion and as there are also no reports of detection of the main drug in biological fluids after oral administration of ABZ to human and animals in various doses [2,6–9,16], it is supposed that the absorbed drug is almost completely converted to ABZ-SO. Thereafter saturation of first pass metabolism and thereafter sulphoxidation process (suggestion (a)) is less likely to have changed in different doses of the main drug. Again, there are reports on the absorption of ABZ to follow a non-saturable process such as passive diffusion both in the stomach [25] and intestine [24] (suggestion (b) rejected). As a result, decrease in F can most likely be a result of decrease in the dissolved fraction of the main drug (suggestion (c)). This was in agreement with the previous suggestion on ABZ to have slow and erratic *in vivo* dissolution [21]. It was also confirmed by *in vitro* results obtained by Jung *et al*. (1998) expressing solubility and not absorption to be the rate limiting step in the absorption of this drug [24]. It is therefore concluded that partial absorption of the main drug is performed after incomplete dissolution of the administered dose of the main drug. As a result, a greater portion of the drug in higher doses of ABZ is excreted unabsorbed resulting in decrease in F and thereby increasing V_d/F and Cl_p/F of ABZ-SO with increasing dose of the main drug. It was also concluded that inconclusive results obtained by Schipper *et al.* [14] resulted due to small sample (subject) size in their study and are in fact due to dose dependent pharmacokinetics of albendazole instead of inter and intra subject variability reported by them. Statistical non-significance in C^*_{max} of different ABZ doses was attributed to inter-subject variations.

As noted previously overall significant difference was observed in AUC^*, $AUMC^*$, Cl_p/F and V_d/F of ABZ-SO in different doses in the repeated measures two-way ANOVA. However, despite obvious diminishing return trend of their values from lower to higher doses, Tukey–Kramer multiple comparisons post hoc test showed significant difference between 400 and 800 mg but no significant change between 800 and 1200 mg doses. These observation can further indicate saturation of dissolution media in the higher doses, *in vivo*. Data could be fitted to rational equation, which is further proof of the above proposition (saturation of the dissolution media).

Conclusions

Pharmacokinetics of main metabolite of ABZ (ABZ-SO) was investigated in human following

administration of three different single oral doses.

The results showed that AUC^* and $AUMC^*$ of ABZ-SO were reduced, whereas V_d/F and Cl_p/F were increased by increasing doses of the parent drug. This was attributed to insufficient in vivo dissolution of ABZ, which in turn results in reduction of fraction of absorbed dose. Therefore, it was concluded that pharmacokinetics of ABZ is dose dependent, ultimately depending on the insufficient in vivo dissolution of the main drug.

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