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PHARMACOKINETICS AND DISPOSITION

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Effect of gender in the disposition of albendazole metabolites in humans

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Abstract The pharmacokinetics of albendazole in different single oral doses (400 mg, 800 mg & 1200 mg) was studied and compared in healthy male and female human volunteers using a double-blind design. The serum levels of albendazole main metabolites (albendazole sulphoxide and albendazole sulphone) were analysed using a modified high-pressure liquid chromatography method. For both metabolites, there was no significant difference in the biological half-life ($t_{1/2}$), time to reach peak concentration (t_{max}) and mean residence time (MRT) between men and women, whereas apparent oral clearance (Cl_p/F) and apparent distribution volume (V_d/F) were less and serum peak concentration (C_{max}), area under the serum concentration–time curve (AUC) and area under the first moment curve (AUMC) were more in women than in men. These observations indicate sex dimorphism in pharmacokinetics of albendazole (observed for albendazole sulphoxide and albendazole sulphone) which were explained on the basis of a change in fraction of the main drug turned to metabolite as a result of more extensive first-pass metabolism of the main drug in the liver of adult female subjects.

Keywords Albendazole · Sex · Gender

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Introduction

Albendazole (ABZ) is a benzimidazole carbamate used as the drug of choice in treatment of echinococcosis [1]. Few studies exist on the disposition, pharmacokinetics, and concentration–effect relationship of ABZ and its metabolites in humans. After oral administration, it is quickly oxidised into its pharmacologically active metabolite albendazole sulphoxide (ABZ-SO) [2]. Further liver oxidative and hydrolytic metabolism produces albendazole sulphone (ABZ-SO_2) and albendazole amino sulphone (ABZ-SO_2-NH_2), respectively, which are thought to be anthelmintically inactive. The scheme of metabolic pathway is shown in Fig. 1. While ABZ possesses a clear therapeutic effect, some pharmacokinetic studies indicate that ABZ-SO is responsible for both anthelmintic and toxic effects [3, 4].

The parent compound is undetectable in the serum after administration to man [5, 6], rat [7], sheep [2], cattle [8] and other species. There is a report on change of pharmacokinetic parameters relative to sex in sheep [9]. Jung et al. (1990) have not observed such a relationship in humans [10]. We intended to further investigate possible effects of gender on these parameters in humans.

Materials and methods

Chemicals

Standard commercial oral dosage forms of ABZ were used. ABZ-SO and ABZ-SO_2 reference standards were donated by SmithKline Beecham (Worthing, UK). ABZ and Mebendazole (MBZ) reference standards were given as gifts by Daroupakhsh Pharmaceutical Co., Iran. Methanol [high-pressure liquid chromatographic (HPLC) grade, Merck] acetonitrile (HPLC grade, Merck) and glacial acetic acid (analytical grade, Merck) were used for HPLC analysis.

Drug administration and blood sampling

Twelve healthy non-smoker human volunteers were separated into two groups based on gender (six women and six men). The subjects

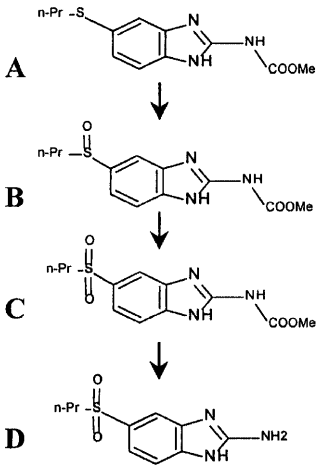

Fig. 1. Proposed main metabolic pathways of ABZ in humans. **a** Albendazole (ABZ). **b** Albendazole sulphoxide (ABZ-SO). **c** Albendazole sulphone (ABZ-SO_2). **d** Albendazole amino-sulphone (ABZ-SO_2-NH_2)

aged 21–44 years and weighed between 52 kg and 85 kg. Men and women averaged about 74 kg and 61 kg, respectively. A complete medical history and physical examination, urinanalysis 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 2 weeks prior to and during the study period. The drug was administered orally in fasting state with 250 ml water. Each group was given one, two or three tablets of ABZ 400 mg as a single dose, with a washout period of 1 week between the treatments. The subjects were given normal standard breakfast, lunch and dinner at 2, 5 and 9 h post-dosing for the three different doses. 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 cannula 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.

HPLC analysis of serum samples

Serum samples were extracted and analysed according to methods described by Zeugin et al. (1990) [11] and Mirfazaelian et al. (2000) [12] with few modifications as follows. Analysis was performed using a Rheodyne 7725i injector fitted with a 50-µl loop, a high-pressure pump (Perkin-Elmer Series 4, USA), a spectrophotometeric detector (Unicam 4225, USA), a flourescence detector (Perkin-Elmer LS-4, USA) and a dual pen recorder (Philips- PM 8252, USA). The stainless-steel column (C_8, Partisil, 5 µm, 100×4.6 mm, Grom, Germany) was preceded by a (C_8, 5 µm, 30×4.6 mm, Pye Unicam, USA) precolumn. Methanol:acetonitrile:acetic acid:water (40:1:10:49) was used as eluent with a flow rate of 0.8 ml/min. The eluent was monitored at 286 nm with UV spectrophotometer for ABZ-SO and MBZ (internal standard) and 286 nm (excitation) –333 nm (emission) for ABZ-SO_2 with a fluorescence spectrophotometer. The assay was accurate and reproducible with a detection limit of 5 ng/ml for ABZ-SO and 2 ng/ml for ABZ-SO_2. Within- and between-day coefficients of variation were less than 10.7% and 9.8%, respectively, calculated at four different concentrations of each metabolite.

Extraction of serum samples was performed by liquid phase extraction with ethyl acetate. The organic phase was then evaporated to dryness at 40°C under a gentle stream of nitrogen. The residue was dissolved in HCl 0.001 m. The samples were further cleaned by washing with n-hexane. The n-hexane phase was discarded, and the sample was re-extracted with ethylacetate after alkalisation. The organic phase was evaporated to dryness as described; the residue was re-dissolved in 300 µl of the HPLC solvent and injected onto the HPLC column.

Pharmacokinetic analysis

Pharmacokinetic parameters were obtained using non-compartmental analysis. Biological half-life ($t_{1/2}$) was calculated using the terminal portion of the plasma concentration–time curve by the following relationship:

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

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

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

$$AUMC_{tn-\infty} = C_n t/k + C_n/k^2 \tag{3}$$

$$AUMC_{t1-\infty} = AUMC_{t1-tn} + AUMC_{tn-\infty} \tag{4}$$

$$MRT = AUC_{0-\infty}/AUC_{0-\infty} \tag{5}$$

Apparent oral clearance (Cl_p/F) of the two metabolites was calculated by division of dose of the main drug (normalised body weight) to $AUMC_{0-\infty}$ for each metabolite. Apparent distribution volume (V_d/F) was resulted by dividing 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 reached to the general circulation; F of ABZ-SO (F_1) was defined as a 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-SO_2 (F_2) was defined as a fraction of the dose of the parent drug absorbed (F_a) and then turned to active metabolite (F_{m1}) and thereafter metabolised to ABZ-SO_2 (F_{m2}) (i.e. $F_2 = F_a \times F_{m1} \times F_{m2} = F_1 \times F_{m2}$).

The derived parameters were subjected to the student's t-test to evaluate the significance of the difference [14]. A P value of less than 0.05 was considered significant.

Results

Serum concentration–time profiles of ABZ main metabolites, ABZ-SO and ABZ-SO_2 in the two groups (men and women) in different doses (400 mg, 800 mg & 1200 mg) are shown in Fig. 2, Fig. 3 and Fig. 4, respectively. Table 1 summarises the pharmacokinetic parameters of ABZ-SO in men and women, and those of ABZ-SO_2 in the two groups (male and female subjects) are demonstrated in Table 2. Table 3 shows ratios of pharmacokinetic parameters of the two metabolites (ABZ-SO/ABZ-SO_2) in men and women. For both metabolites, there was no significant difference in the $t_{1/2}$ time to reach peak concentration (t_{max}) and mean residence time (MRT) (with two exceptions), whereas Cl_p/F and V_d/F were less and serum peak concentration (C_{max}), AUC and AUMC were more in women than in men.

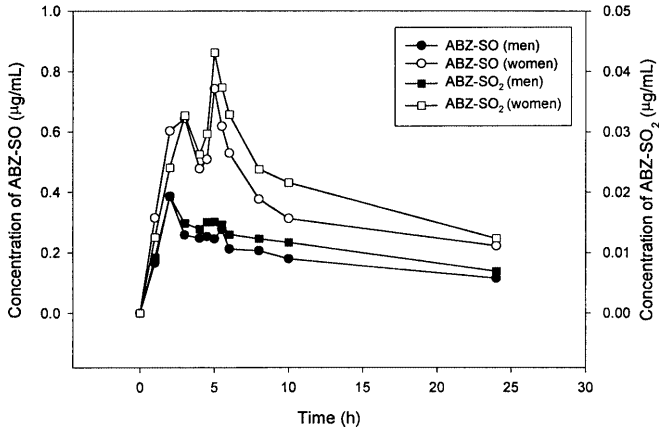

Fig. 2. Serum profiles of albendazole sulphoxide (ABZ-SO) and albendazole sulphone ($ABZ\text{-}SO_2$) in volunteers taking an oral single dose of 400 mg (mean data)

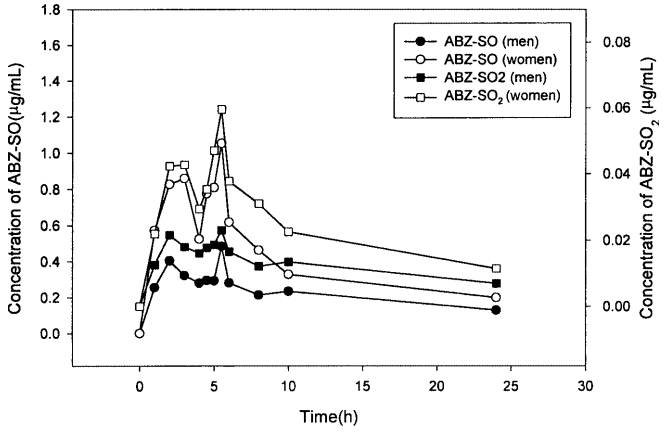

Fig. 3. Serum profiles of albendazole sulphoxide (ABZ-SO) and albendazole sulphone ($ABZ\text{-}SO_2$) in volunteers taking an oral single dose of 800 mg (mean data)

Discussion

The values of the pharmacokinetic parameters of ABZ metabolites (men) were in good general agreement with previous studies (mostly male subjects) [6, 15, 16].

Effect of gender on ABZ-SO disposition

Evaluation of pharmacokinetic parameters of ABZ-SO showed increase in C_{max}, AUC and AUMC and reduction in Cl_p/F_1 and V_d/F_1 in women compared with men instead of the expected no change in these parameters in homogeneous metabolism. For example, considering a 400-mg dose, mean C_{max} was about 465 ng/ml in men and 909 ng/ml in women, and AUC was about 5 μg h/ml and 10 μg h/ml in men and women, respectively. AUMC was about 50 μg h^2/ml in men and 100 μg h^2/ml in women at the 400-mg dose. Mean Cl_p/F_1 was about 0.7 l/h/kg in men and 0.4 l/h/kg in women, and V_d/F_1 was about 17 l/kg and 12 l/kg in men and women, respectively. These differences were observed in all the dose ranges studied (i.e. 400, 800 & 1200 mg, Table 1). These findings can indicate heterogeneity of the sulphoxidation process and its dependence on gender of the subjects.

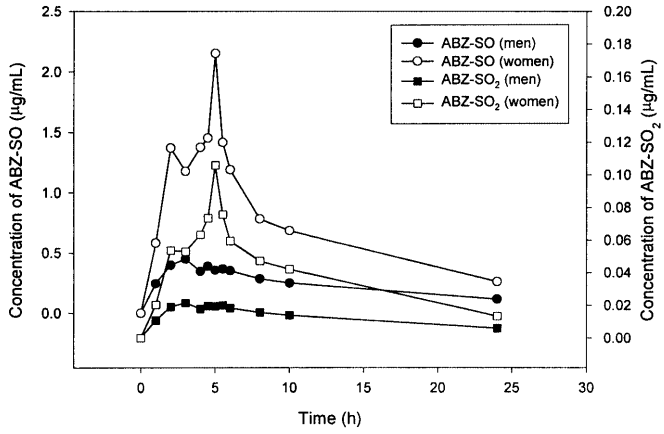

Fig. 4. Serum profiles of albendazole sulphoxide (ABZ-SO) and albendazole sulphone ($ABZ\text{-}SO_2$) in volunteers taking an oral single dose of 1200 mg (mean data)

Jung et al. (1990) have reported no significant difference in steady-state plasma concentration in male and female patients [10]. However, noting their reported values, plasma concentration of ABZ-SO was 1.3 μg/ml in women and 0.7 μg/ml in men. Therefore, the statistical non-significance in their result could be a result of inter-subject variability. We also observed high variations between our subjects, which is in concordance with previous studies [5, 6, 10, 17, 18]. Inter-subject variations can be attributed to the low F (about 1%) in humans [19].

A decrease in C_{max} and AUC_{0-24} in men relative to women could be caused by a female subject's lower weight. However as Cl_p/F_1 and V_d/F_1 in women were less than in men, another reason can be proposed (though possibility an effect of subject's weight cannot be ruled out); reduced female Cl_p/F_1 and V_d/F_1 could be a result of either decrease in clearance (Cl_p) and distribution volume (V_d) or increase in the fraction of dose transformed to the metabolite and reached the general circulation (F_1). The increase in Cl_p necessitates change in $t_{1/2}$ or V_d. As noted above, biological $t_{1/2}$ of ABZ-SO remained statistically unchanged in the two groups. There is also a moderate protein binding reported for this metabolite in the literature (63–65%) [20] which rejects the possibility of heterogeneous V_d as a result of sex dimorphism in plasma protein binding. Therefore, decrease of Cl_p/F_1 and V_d/F_1 can be a result of an increase in the fraction of the main drug metabolised and reached the general circulation (F_1). Increase in F_1 can itself be either as a result of (a) increased absorption of the main drug (F_a) or (b) more sulphoxidation in women than men (F_{m1}). We found no report of difference in absorption of the pharmaceuticals in male and female

Table 1. Pharmacokinetic parameters of albendazole sulphoxide (ABZ-SO) in volunteers taking different oral single doses (400, 800 & 1200-mg tablets). Mean ± SD, *n.s.* non-significant

Parameter	400-mg dose			800-mg dose			1200-mg dose		
	Men	Women	*t*-test	Men	Women	*t*-test	Men	Women	*t*-test
Area under the serum concentration–time curve$_{0-24}$ (μg h/ml)	5.0 (2.8)	10.2 (5.7)	n.s.	5.5 (1.74)	9.4 (4.3)	n.s.	5.2 (1.3)	17.7 (8.4)	0.006
Area under the first moment curve$_{0-24}$ (μg h^2/ml)	51.0 (30.4)	98.6 (54.4)	n.s.	53.498 (6.8)	81.6 (31.0)	n.s.	46.8 (14.2)	151.6 (61.7)	0.003
Mean residence time (h)	26.2 (14.3)	24.3 (11.9)	n.s.	24.8 (8.2)	13.4 (2.6)	n.s	18.0 (6.9)	15.5 (4.9)	n.s.
Half-life (h)	16.3 (13.2)	16.7 (10.1)	n.s.	16.6 (4.9)	7.5 (3.9)	n.s.	12.2 (6.0)	10.5 (3.0)	n.s.
Serum peak concentration (ng/ml)	464.8 (279.1)	908.9 (359.0)	0.04	525.5 (210.3)	1333.1 (873.7)	0.04	523.2 (161.7)	2562.1 (2289.7)	0.04
Time to reach peak concentration (h)	2.8 (1.2)	5.1 (3.6)	n.s.	3.0 (2.0)	3.8 (2.2)	n.s.	3.3 (1.7)	4.3 (1.6)	n.s.
Apparent oral clearance (l/h/kg)	0.7 (0.4)	0.4 (0.2)	n.s.	1.4 (0.6)	1.1 (0.6)	n.s.	2.7 (1.4)	1.0 (0.4)	0.04
Apparent distribution volume (l/kg)	17.3 (17.4)	11.8 (5.8)	n.s.	31.1 (8.6)	10.6 (5.2)	0.005	39.3 (12.9)	13.6 (7.3)	0.01

Table 2. Pharmacokinetic parameters of albendazole sulphone (ABZ-SO$_2$) in volunteers taking different oral single doses (400, 800 & 1200-mg tablets). Mean ± SD, *n.s.* non-significant

Parameter	400-mg dose			800-mg dose			1200-mg dose		
	Men	Women	*t*-test	Men	Women	*t*-test	Men	Women	*t*-test
Area under the serum concentration–time curve$_{0-24}$ (μg h/ml)	0.3 (0.2)	0.7 (0.5)	n.s.	0.3 (0.1)	0.5 (0.3)	n.s.	0.3 (0.1)	0.9 (0.5)	0.01
Area under the first moment curve$_{0-24}$ (μg h^2/ml)	3.2 (1.9)	6.7 (4.9)	n.s.	3.1 (1.0)	4.9 (2.5)	n.s.	2.6 (0.7)	8.3 (4.0)	0.008
Mean residence time (h)	22.9 (11.1)	20.3 (7.2)	n.s.	25.7 (14.4)	13.8 (2.9)	n.s.	16.8 (5.8)	17.1 (8.4)	n.s.
Half-life (h)	17.2 (7.1)	13.2 (6.0)	n.s.	17.4 (9.3)	7.5 (3.3)	n.s.	11.2 (5.3)	11.1 (5.7)	n.s.
Serum peak concentration (ng/ml)	24.4 (11.8)	57.3 (42.1)	n.s.	29.0 (12.1)	70.5 (46.8)	0.04	27.0 (9.09)	114.1 (108.2)	n.s.
Time to reach peak concentration (h)	3.8 (3.1)	6.5 (3.1)	n.s.	2.8 (1.4)	4.0 (1.8)	n.s.	3.3 (1.7)	4.5 (1.1)	n.s.
Apparent oral clearance (l/h/kg)	16.5 (8.8)	8.1 (3.3)	n.s.	24.4 (11.4)	20.6 (14.1)	n.s.	49.3 (22.5)	19.1 (8.1)	0.04
Apparent distribution volume (l/kg)	341.3 (184.6)	165.7 (87.9)	n.s.	536.5 (203.6)	212.5 (84.5)	0.02	681.9 (209.9)	285.3 (220.8)	0.04

subjects, and therefore these observations can most likely be attributed to more extensive first-pass metabolism of the parent drug in women than in men. The possibility of these differences between men and women due to entero-hepatic recycling is not likely, due to low amounts of ABZ-SO detected in human bile [6, 21].

Lack of significant differences in AUC_{0-24}, $AUMC_{0-24}$, Cl_p/F_1, Vd/F_1 of ABZ-SO of 400-mg dose and AUC_{0-24}, $AUMC_{0-24}$, Cl_p/F_1, of ABZ-SO of 800-mg dose between men and women were attributed to inter-subject variations discussed previously [5, 6, 10, 22, 23]. The above observations are in agreement with enzyme studies performed previously; Rawden et al. (2000) have suggested that cytochrome P_{450} (principally CYP3A4) is the major contributor in ABZ-SO production in the adult human liver [24]. CYP3A4 isoenzyme composes approximately 60% of the cytochrome P_{450} system [25]. Sex dimorphism in CYP3A4 expression is reported based on several medicinal substrates of CYP3A4; i.e. greater activity of this isoenzyme was noted in women than men [26, 27, 28]. Therefore it can be concluded that ABZ-SO production is a gender-dependent process which is performed more extensively in women than men.

Effect of gender on ABZ-SO$_2$ disposition

Again, evaluation of pharmacokinetic parameters of ABZ-SO$_2$ showed an increase of C_{max}, AUC and AUMC and reduction of Cl_p/F_2 and V_d/F_2 in women compared with men instead of the expected no change in these parameters in homogeneous metabolism. For example, a 400-mg dose mean C_{max} was 24 ng/ml in men and 57 ng/ml in women, and AUC was about 0.3 μg h/ml and 0.7 μg h/ml in men and women, respectively.

Table 3. Ratio of pharmacokinetic parameters of albendazole sulphoxide to albendazole sulphone (ABZ-SO/ABZ-SO_2) in volunteers taking different oral single doses (400, 800 & 1200-mg tablets). Mean ± SD. Ratio of parameters are dimensionless. Units refer to the parameters themselves, *n.s.* non-significant

Parameter	400-mg dose			800-mg dose			1200-mg dose		
	Men	Women	*t*-test	Men	Women	*t*-test	Men	Women	*t*-test
Area under the serum concentration–time $curve_{0-24}$ (μg h/ml)	16.4 (2.4)	16.3 (2.6)	n.s.	17.3 (3.1)	18.3 (3.0)	n.s.	18.3 (2.0)	19.9 (2.6)	n.s.
Area under the first moment $curve_{0-24}$ (μg h^2/ml)	16.5 (3.2)	15.8 (2.5)	n.s.	17.6 (3.7)	17.7 (3.2)	n.s.	18.2 (2.0)	18.9 (2.5)	n.s.
Mean residence time (h)	1.1 (0.3)	1.2 (0.3)	n.s.	1.1 (0.3)	1.0 (0.1)	n.s.	1.1 (0.1)	1.0 (0.2)	n.s.
Half-life (h)	1.2 (0.3)	1.2 (0.3)	n.s.	1.1 (0.3)	1.0 (0.1)	n.s.	1.1 (0.1)	1.0 (0.2)	n.s.
Serum peak concentration (ng/ml)	18.1 (3.0)	18.6 (5.1)	n.s.	18.4 (3.0)	19.5 (5.8)	n.s.	19.6 (1.6)	23.4 (2.0)	n.s.
Time to reach peak concentration (h)	0.9 (0.2)	0.8 (0.3)	n.s.	1.1 (0.4)	0.9 (0.3)	n.s.	1.0 (0.0)	0.9 (0.2)	n.s.
Apparent oral clearance [$\times 10^3$] (l/h/kg)	57.9 (16.4)	55.9 (13.5)	n.s.	60.6 (16.4)	53.6 (10.7)	n.s.	53.6 (5.5)	49.9 (6.0)	n.s.
Apparent distribution volume [$\times 10^3$] (l/kg)	66.9 (3.0)	68.7 (19.6)	n.s.	60.6 (12.6)	53.5 (16.3)	n.s.	57.9 (7.5)	51.8 (15.8)	n.s.

AUMC was about 3.2 μg h^2/ml in men and 6.7 μg h^2/ml in women at the 400-mg dose. Mean Cl_p/F_2 was about 17 l/h/kg in men and 8 l/h/kg in women, and Vd/F_2 was about 341 l/kg and 166 l/kg in men and women, respectively, at the 400-mg dose. These differences were observed at all the dose ranges studied (i.e. 400, 800 & 1200 mg; Table 2). These findings indicate that ABZ-SO_2 pharmacokinetics is a sex-dependent process.

The same reasoning would be true for evaluation of comparison of pharmacokinetics of ABZ-SO2 in men and women for ABZ-SO. Again, though the influence of female subjects' lower weights on parameters such as C_{max} and AUC_{0-24} cannot be ruled out, reduced Cl_p/F_2 and V_d/F_2 in women compared with men for ABZ-SO_2 is assumed to be a result of an increase in F of ABZ-SO_2 (F_2), which in turn can either be as a result of (i) increase in sulphonation of ABZ-SO (F_{m2}) and/or (ii) increase in F of ABZ-SO (F_1) in females compared with the male subjects.

Ratios of pharmacokinetic parameters in ABZ-SO to their relative ABZ-SO_2 parameter (ABZ-SO/ABZ-SO_2) were not significantly different between male and female subjects in various doses studied. This indicates that sulphonation of ABZ-SO is not a sex-dependent process; in other words, the sulphonation process has the same rate and extent in men as in women in the dose range studied (suggestion i rejected). Therefore, as previously discussed, sex dimorphism in the pharmacokinetics of ABZ-SO_2 can be related to sex dimorphism in ABZ-SO pharmacokinetics which is itself as a result of more CYP3A4 content and expression in female than male human subjects.

Non-significant differences in AUC_{0-24}, $AUMC_{0-24}$, C_{max}, Cl_p/F_2, Vd/F_2 of ABZ-SO_2 of the 400-mg dose, AUC_{0-24}, $AUMC_{0-24}$, Cl_p/F_2, of ABZ-SO_2 of the 800-mg dose and C_{max} of the 1200-mg dose between men and women were attributed to inter-subject variations discussed above [5, 6, 10, 22, 23].

Conclusions

The pharmacokinetics of two main metabolites of ABZ (ABZ-SO & ABZ-SO_2) was investigated in healthy male and female human subjects following administration of different single oral doses (400 mg, 800 mg & 1200 mg). For both metabolites, Cl_p/F and V_d/F were less in women, and C_{max}, AUC and AUMC were more in women than men. These observations indicate sex dimorphism in pharmacokinetics of albendazole (observed for albendazole sulphoxide and albendazole sulphone), which were explained on the basis of a change in fraction of the main drug turned to metabolite (ABZ-SO) in the first-pass metabolism as a result of more extensive metabolism of the main drug in the liver of adult female subjects. The above conclusions were confirmed by the enzyme studies reporting female-dominant expression of CYP3A4 in adult humans.

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