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Increased systemic bioavailability of albendazol when administered with surfactants in rats

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Summary

This work describes the determination of the plasma concentrations of albendazol sulfoxide (ABZ.SO) after administration of single oral doses of albendazol (ABZ) using surfactants as vehicles (Tween 80 and sodium taurocholate). The pharmacokinetic parameters AUC, C_{max} and t_{max} were affected by the use of surfactants. The results showed higher plasma levels of ABZ.SO and the ratio, AUC/initial dose, was 60–100-times greater in the presence of surfactants.

Albendazol (ABZ; methyl-(5-propylthio-1H-benzimidazol-2-yl) carbamate) is a broad-spectrum anthelmintic effective in the treatment of hydatidosis (McCraken and Lipkowitz, 1990).

Different pharmacokinetic studies of ABZ showed that there occur individual variations in plasma levels attained after oral doses due, among other factors, to the poor solubility of ABZ (Marriner et al., 1986). When ABZ is administered orally, the original compound is practically undetectable in blood in both humans and different species, ABZ.SO being the compound which appears mainly in blood and tissues. This metabolite also presents anthelmintic activity. Prolonged treatments (usually oral doses of 5–10 mg/kg per day for man and 10–20 mg/kg for other species) caused hepatic anomalies (Gil Grande et al., 1987).

Previous studies (Del Estal et al., 1991, 1993) have proved that surfactants increase the intestinal absorption of ABZ. The amphiphilic nature of surfactants enables them to solubilize lipophilic compounds, which may contribute to increased gastrointestinal absorption of the drugs (Poelma et al., 1990). The aim of this study was to determine the plasma levels of ABZ and ABZ.SO, following single oral doses of 0.01 mg/kg ABZ, when 5% Tween 80 and 38 mM STC were used as vehicles, this dose of ABZ being about 1000-times lower than those usually administered.

The experimental animals used were male Wistar rats weighing from 250 to 300 g, fed on commercial chow, and kept under controlled housing conditions. Administration of the doses

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was carried out at the same time (9–10 a.m.). ABZ and ABZ.SO were supplied by Smithkline Beecham, S.A. (Madrid, Spain). Polysorbate 80 (Tween 80) (polyoxyethylene sorbitol monooleate) and taurocholic acid sodium salt (STC) (98% purity) were purchased from Sigma Chemical Co. (Madrid, Spain). ABZ was solubilized in 38 mM STC or in 5% Tween 80 at a concentration of 0.0025 mg ml^{-1} and administered in a single oral dose of 0.01 mg/kg body weight, by intragastric tube (approx. 1.5 ml per animal). The same dose in saline suspension was administered to control rats.

Blood obtained from the cannulated carotid artery was collected at 0.5, 1, 2, 4, 6, 8, and 10 h after administration, using four experimental animals for each sampling time. Determination of the drug (ABZ) and its metabolite (ABZ.SO) in plasma samples was performed by high-performance liquid chromatography (HPLC), the basic procedure being as described by Del Estal et al. (1991). Under these chromatographic conditions, the retention time for ABZ.SO was 3.90 min and for ABZ 17 min. Detection limits of the method were 30 and 60 ng ml^{-1} for ABZ and ABZ.SO, respectively. The method was optimized to reach detection limits up to 10 ng ml^{-1} for both compounds.

The pharmacokinetic parameters C_{max}, t_{max} and AUC were obtained from the graphic representation of plasma levels ($\mu g\ ml^{-1}$) vs time (h). The area under the curve ($AUC_{(0-10\ h)}$) was calculated using the trapezoidal method.

Pharmacokinetic constants were compared using Student's t-test, with a significance level of $P < 0.05$.

Since ABZ as the original compound appears at undetectable concentrations in blood, all results refer to levels of ABZ.SO. Tables 1 and 2 show the changes in plasma levels of ABZ.SO following administration of a single oral dose of ABZ of 0.01 mg/kg body weight, in a vehicle of Tween 80 (Table 1) or STC (Table 2). On the basis of on these data, the maximum concentration of ABZ.SO in plasma (C_{max}), the time when this concentration appears (t_{max}) and the area under the curve (AUC_{0-10}) were calculated; these results are listed in Table 3.

TABLE 1

Plasma levels of ABZ.SO after administration of ABZ with 5% Tween 80

Time (h)	[ABZ.SO] (μg/ml)				mean ± S.D.
	1	2	3	4	
0.5	0.118	0.123	0.118	0.133	0.123 ± 0.007
1	0.159	0.185	0.174	0.185	0.176 ± 0.011
2	0.192	0.160	0.190	0.160	0.175 ± 0.015
4	0.250	0.303	0.261	0.230	0.261 ± 0.031 [a]
6	0.190	0.225	0.223	0.190	0.207 ± 0.017
8	0.196	0.172	0.136	0.170	0.169 ± 0.021
10	0.108	0.132	0.138	0.170	0.137 ± 0.022

ABZ.SO plasma levels (μg/ml) as determined by HPLC after the administration of an oral dose of ABZ (0.01 mg/kg) in Tween 80 (5%). Data are given as individual values from four different experiments and their respective means ± S.D. Sampling time following administration is also included. [a] $P < 0.05$.

The results show that when Tween 80 is used the t_{max} is approx. 4 h; however, when STC is used this time is reduced to about 2 h. These t_{max} values would correspond to the apparent absorption rate constant (K_a) obtained when using both surfactants: 1.300 ± 0.230 h^{-1} with Tween 80 and 2.810 ± 0.116 h^{-1} with STC (Del Estal et al., 1991). With regard to C_{max}, the values obtained were 0.261 ± 0.031 $\mu g\ ml^{-1}$ with Tween 80 and 0.242 ± 0.027 $\mu g\ ml^{-1}$ with STC, thus showing no

TABLE 2

Plasma levels of ABZ.SO after administration of ABZ with 38 mM sodium taurocholate

Time (h)	[ABZ.SO] (μg/ml)				mean ± S.D.
	1	2	3	4	
0.5	0.152	0.139	0.163	0.143	0.149 ± 0.009
1	0.155	0.143	0.156	0.136	0.147 ± 0.008
2	0.265	0.208	0.220	0,272	0.242 ± 0.028 [a]
4	0.153	0.147	0.160	0.151	0.153 ± 0.005
6	0.140	0.135	0.134	0.137	0.136 ± 0.002
8	0.148	0.148	0.116	0.152	0.141 ± 0.014
10	0.159	0.141	0.135	0.145	0.145 ± 0.009

ABZ.SO plasma levels (μg/ml) as determined by HPLC after the administration of an oral dose of ABZ (0.01 mg/kg) in sodium taurocholate (38 mM). Data are given as individual values from four different experiments and their respective means ± S.D. Sampling time following administration is also included. [a] $P < 0.05$.

TABLE 3

Pharmacokinetic parameters after administration of ABZ with Tween 80 and sodium taurocholate

ABZ + Tween		ABZ + STC	
C_{max} (μg/ml)	AUC (μg ml^{-1} h)	C_{max} (μg/ml)	AUC (μg ml^{-1} h)
0.250	1.917	0.265	1.631
0.303	1.973	0.208	1.492
0.261	1.853	0.220	1.484
0.230	1.796	0.272	1.607

Individual values of maximum concentration of ABZ.SO in plasma (C_{max}), and area under the concentration-time curve (AUC), obtained with the different plasma levels (between 0 and 10 h) (see Table 1 (Tween) and Table 2 (STC) for these values) following an oral dose of ABZ of 0.01 mg/kg using Tween 80 at 5% and STC 38 mM as vehicles.

significant differences. However, for the $AUC_{(0-10)}$ value, there were statistically significant differences between surfactants. The $AUC_{(0-10)}$ in the presence of Tween 80 was 1.885 ± 0.067 μg ml^{-1} h, whereas the corresponding value with STC was 1.554 ± 0.066 μg ml^{-1} h. Therefore, the bioavailability of ABZ with Tween 80 was significantly greater ($P < 0.05$).

The $AUC_{(0-10)}$ value for ABZ.SO we obtained in control rats was 0.091 ± 0.031 μg ml^{-1} h, which is about 20-times smaller than the AUC values of STC and Tween, the C_{max} in control rats was 0.014 ± 0.04 μg ml^{-1} and t_{max} was approx. 4–6 h.

These results are in accordance with those reported by other authors in similar experiments. Thus, following administration of an oral dose of ABZ of 10.6 mg/kg in rats, Suohaili et al. (1988) obtained approximate values of the $AUC_{(0-18)}$ of 30 μg ml^{-1} h and an approximate $AUC_{(0-9)}$ of 20 μg ml^{-1} h. Delatour et al. (1990), after oral administration in rats of 10 mg/kg of ABZ, determined an approximate $AUC_{(0-18)}$ of 39.2 μg ml^{-1} h and an approximate $AUC_{(0-9)}$ of 24 μg ml^{-1} h.

Since the oral dose used (0.01 mg/kg) is approx. 1000-times lower than that used previously by others, we were able to calculate the corresponding $AUC_{(0-9)}$/dose ratios, and to compare the present results. This value would be about 0.0019 h kg ml^{-1} (data of Souhaili et al. 1988), and 0.0024 h kg ml^{-1} (data of Delatour et al. 1990). The corresponding values ($AUC_{(0-10)}$/dose) with our results were about 0.009 h kg ml^{-1} for control, and 0.189 h kg ml^{-1} with Tween 80 and 0.155 h kg ml^{-1} with STC. This relation is higher than the corresponding values without surfactants, and indicates that the administration of ABZ solubilized with these surfactants makes the relative quantity of the drug reaching plasma much greater, thus leading to more efficient bioavailability.

On the other hand, the t_{max} values obtained from 3 to 6 h without surfactants were slightly shorter, from 2 to 4 h, due to the use of the surfactants as vehicles for ABZ. Regarding the C_{max}, we obtained values ranging from 2.8 to 3.5 μg/ml of ABZ.SO, following the administration of an oral dose of ABZ of 10–10.6 mg/kg, 0.014 μg/ml in control rats and 0.24–0.26 μg/ml with the use of surfactants, at doses of ABZ of 0.01 mg/kg. Therefore, the parameters AUC, C_{max} and t_{max} are improved by the use of surfactants solubilizing ABZ.

The results described in this paper show that the absorption of ABZ is improved and thus that better use can be made of the dose administered in the presence of surfactants. Taurocholate improves the absorption of ABZ at least in terms of the speed; the question as whether Tween 80 or STC is the most effective can only be resolved after carrying out a clinical trial, which would enable us to decide which is the most suitable surfactant in each case.

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