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Enantioselective Kinetic Disposition of Albendazole Sulfoxide in Patients With Neurocysticercosis

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ABSTRACT The enantioselectivity of the kinetic disposition of albendazole sulfoxide (ASOX) was investigated in 18 patients with neurocysticercosis treated with a multiple dose regimen of albendazole for 8 days (5 mg/kg every 8 h). Serial blood samples were collected on the eighth day of treatment during the last dose interval, with prorogation up to 12 h. Albendazole sulfone (ASON) and enantiomers of ASOX were analyzed in plasma samples by HPLC using a Chiralpak® AD column and detection by fluorescence. The pharmacokinetic parameters showing statistically significant differences between the (+) ASOX and (–) ASOX enantiomers are presented as respective means (95% CI) as follows: maximum plasma concentration, C_{max} = 301.6 (179.7–423.5) vs 54.9 (21.9–87.9) ng · ml^{-1}; elimination half-life, $t_{1/2}$ = 5.2 (4.1–6.3) vs 3.3 (2.8–3.8) h, area under the plasma concentration-time curve, AUC_{ss}^{0-8} = 1719.2 (978.6–2459.8) vs 261.4 (102.9–419.8) ng · h · ml^{-1} and apparent clearance, Cl/fm = 5.8 (3.8–7.8) vs 54.0 (35.2–72.7) l · h^{-1} · kg^{-1}. The mean value of 9.2 (7.6–10.9) for the $AUC^{0-8}_{(+)\text{-ASOX}}/AUC^{0-8}_{(-)\text{-ASOX}}$ ratio demonstrated plasma accumulation of the (+) enantiomer. Sulfone formation capacity, expressed by the AUC_{ss}^{0-8} ratio ASON/ASOX + ASON, was 8.0 (7.0–8.9). The present data indicate enantioselectivity in the kinetic disposition of ASOX in patients with neurocysticercosis. *Chirality 11:218–223, 1999.*

KEY WORDS: albendazole sulfoxide; enantioselectivity, pharmacokinetics, cysticercosis, metabolism; patient

Albendazole, methyl (5-[propylthio]-1H-benzimidazol-2-yl) carbamate, is a broad-spectrum antihelmintic agent used clinically for the treatment of neurocysticercosis. Human cysticercosis, the invasion of body tissues by the larvae of the pork tapeworm (*Taenia solium*), mainly affects countries in Latin America, Asia, Africa, and certain areas of the United States with a large immigrant population.[1,2,3] In Brazil, the disease in the states of São Paulo, Paraná, Minas Gerais, and Goiás is considered to be endemic.[4]

Albendazole is essentially eliminated by metabolism (Fig. 1); S-oxidation products (the sulfur atom of the benzimidazole group in the S position in the molecule) represented by albendazole sulfoxide (ASOX) and albendazole sulfone (ASON) are the major metabolites.[5] Previous studies have demonstrated that, in rats, the antihelmintic activity depends on the ASOX metabolite.[6]

The high presystemic elimination of albendazole in rodents, ruminants, and man results in plasma concentrations of unchanged albendazole below the quantification limits of the chromatographic methods currently available, i.e., less than 10 ng · ml^{-1} plasma.[7,8] This fact limits pharmacokinetic studies to S-oxidation metabolites only.

Few studies are available about the kinetic disposition of ASOX. Jung et al. (1992)[9] investigated the kinetic disposition of ASOX in 8 patients with neurocysticercosis treated with albendazole for 8 days (15 mg/kg/day). The maximum plasma concentration (C_{max}) of ASOX ranged from 0.5 to 3.0 μg · ml^{-1} and the elimination half-life ranged from 6 to 15 h. ASOX binding to plasma protein is relatively low, with values of approximately 70% having been reported by Marriner et al. (1986).[8] Considering that albendazole usually is not detected in plasma, the absorption rate constant expresses not only albendazole absorption but also its metabolism to ASOX. The pharmacokinetic parameter was reduced by 72% in patients with hydatid disease and extrahepatic cholestasis, suggesting that bile is required for the rapid absorption of albendazole.[10] Foods rich in fat may also favor albendazole absorption and represent one of the

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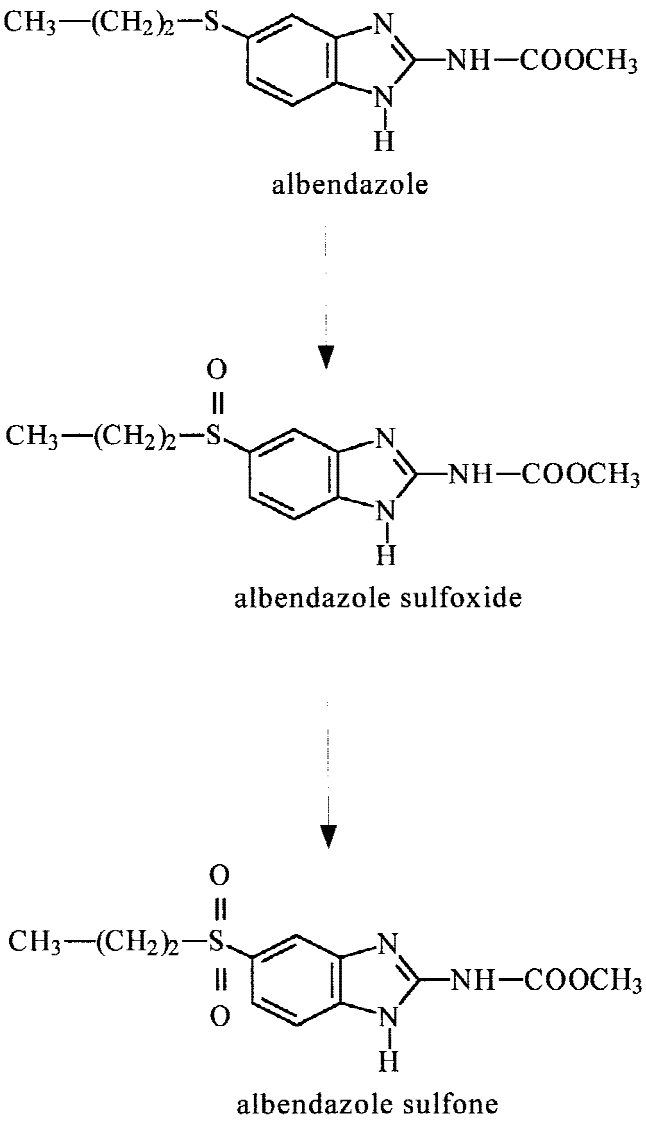

Fig. 1. Albendazole metabolism.

factors underlying interindividual variability in the plasma concentrations of ASOX.[8,11]

The R-SO-R′ group of ASOX contains a center of asymmetry, with the production of (+)-ASOX and (–)-ASOX enantiomers. However, no data are available about the absolute configuration of the enantiomers or their biological activities.[6] Delatour et al. (1991a)[12] investigated enantioselectivity in the metabolism of a single dose of albendazole administered to four healthy volunteers. These authors reported that the (+)/(–) ratios of the plasma concentrations of ASOX reveal the accumulation of (+)-ASOX (values of 1 to 13 up to 10 h after administration). The (+) enantiomer also dominates in the plasma of dogs and goats, whereas the opposite is observed in rats.[7,12–14]

The (+) and (–) enantiomers of ASOX are oxidized to ASON, a nonchiral metabolite that makes no contribution to the therapeutic efficacy of albendazole. It is probable that enantiomer ratios of ASOX differing from one are also a consequence of the selective metabolism of one ASOX enantiomers.[12] S-Oxidation to the corresponding sulfone plays an important role in the inactivation and elimination of albendazole sulfoxide.

The present study is an investigation of enantioselectivity in the kinetic disposition of ASOX and describes the metabolism of ASOX to ASON in patients with neurocysticercosis being treated with albendazole in a multiple-dose regimen.

PATIENTS, MATERIALS, AND METHODS

Patients

Eighteen patients (9 males and 9 females) with active neurocysticercosis aged 14 to 67 years (mean = 41 years), weighing 47 to 90 kg (mean = 64 kg) gave informed consent to participate in the study. The diagnosis was confirmed by computed tomography and ELISA of cerebrospinal fluid. Hepatic and renal function were evaluated by clinical and laboratory tests. The individual patient data are presented in Table 1. Patients received albendazole p.o. (Zentel®, tablets; Smithkline Beecham Laboratories Ltd., Rio de Janeiro, Brazil) 3 times a day for 8 days (5 mg/kg every 8 h). Serial venous blood samples were obtained after administration of the last dose on day 8 at zero h (predose) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, and 12 h. The plasma obtained after centrifugation at 1,800*g* for 20 min was stored at –20°C. Approval for the study was obtained from the Ethics Committee of the local university hospital—University of São Paulo (Ribeirão Preto, Brazil) where all patients were hospitalized during the study.

Analytical Assay

Plasma samples were analyzed by HPLC using a fluorescence detector (λ_{exc} = 280 nm; λ_{em} = 320 nm) and a chiral column (Chiralpak® AD, 4.6 mm × 250 mm, 10 µm particle size; Chiral Technologies Inc., Exton, PA) as described previously by Lanchote et al. (1998).[15] Reference *rac*-albendazole sulfoxide (99.4%) and albendazole sulfone (99.8%) were kindly supplied by Robert Young & Co. Ltd., Glasgow, Scotland. Briefly, (+)-ASOX, (–)-ASOX, and ASON were extracted from 500 µl plasma samples supplemented with 200 µl of a sodium metabisulfite solution (4 mg/ml). The samples were added with ethyl acetate (3 ml), submitted to mechanical shaking for 20 min (200 cycles/min) and then centrifuged at 1,800*g* for 5 min. The tubes were frozen and the organic layers (2 ml) were transferred to clean tubes and evaporated to dryness under a nitrogen stream. The residues were reconstituted in 50 µl of the mobile phase (81:14.25:4.75, v/v/v, mixture of hexane:isopropanol:ethanol) and chromatographed. The column was operated at ambient temperature at a flow rate of 1.2 ml/min. The elution order for metabolites was (+)-ASOX (13.7 min), (–)-ASOX (21.6 min), and ASON (25.7 min). The stereoselective factor (α) of 1.7 was calculated using the equation $\alpha = k_2'/k_1'$ where k_1' and k_2' are the capacity factors for the first and second enantiomers eluted, respectively. Linear standard curves were obtained in the concentration range of 5–2,500 ng/ml for ASOX enantiomers and the range 1 to 500 ng/ml for ASON. The within-day and between-days coefficients of variation were less than 10.0% for the three compounds.

TABLE 1. Individual characteristics of the patients investigated (n = 18)

Patient	Sex[a]	Age (years)	Weight (kg)	Associated drugs
AAT	M	46	80.0	Nifedipine phenytoin, ranitidine, dextrochlorpheniramine
AEP	M	42	90.0	Phenytoin, dexamethasone, ranitidine
CRF	M	39	62.5	Phenytoin
DR	M	24	64.9	Dexamethasone, phenytoin
EMSC	F	31	51.0	Phenytoin
GJF	M		49.7	Carbamazepine, phenytoin, ranitidine
JB	M	67	59.7	Metoprolol, carbamazepine, dextrochlorpheniramine
JR	M	48	63.0	Cimetidine, dexamethasone, phenytoin
LC	F	14	52.8	Carbamazepine
MARS	F	39	62.2	Acetylsalicyclic acid
MT	M	64	50.0	Lorazepam, ranitidine, phenytoin
NAZ	F	46	83.0	Dexamethasone, ranitidine
NMF	F	31	59.7	Dexamethasone, ranitidine, carbamazepine, diazepam
PT	M	42	75.0	Dextrochlorpheniramine, phenytoin
RAF	F	41	66.7	Dexamethasone, ranitidine, amitryptiline
TCA	F	54	46.7	Carbamazepine, dextrochlorpheniramine
WMM	F	22	67.0	Dexamethasone, phenytoin
ZFP	F	40	72.0	Carbamazepine, ranitidine, dexamethasone
Mean (±SEM)		40.6 (±3.4)	64.2 (±2.9)	

[a]F, female; M, male.

Pharmacokinetic and Statistical Analysis

The maximum plasma concentration (C_{max}) and time to maximum concentration (t_{max}) were obtained directly by inspection of the data for each patient. The area under the plasma concentration-time curve from 0 to 8 h ($AUC_{ss}^{0–8}$) was determined using the linear trapezoidal method. Apparent clearance (Cl/fm, in which fm is the fraction of the administered dose of drug that enters the general circulation as metabolite) was calculated by dividing the albendazole dose by the AUC for metabolite. The apparent clearance of metabolite was further adjusted for body weight and corrected for the albendazole dose from the molecular weight of ASOX or ASON. Parameters such as terminal half-life ($t_{1/2}$), elimination rate constant (Kel), formation half-life ($t_{1/2}f$), and formation rate constant (Kf) were estimated as described previous.[17] The results are expressed as the mean ± 95% CI and as the median. Differences between data for (+)- and (–)-ASOX were analyzed by the Student's *t*-test for paired data, accepting $P \leq 0.05$ as significant.

RESULTS AND DISCUSSION

In the present investigation, albendazole metabolism was evaluated in the steady-state during the 8-h dose interval, with discontinuation of the subsequent doses and prorogation of collection up to 12 h to evaluate the phase of terminal elimination of the metabolites. Steady-state was ensured by the administration of multiple albendazole doses over 8 days of treatment.

The pharmacokinetic parameters derived from the plasma concentrations of (+)-ASOX and (–)-ASOX are presented in Table 2. The maximum plasma concentrations (C_{max}) (mean values of 301.6 ng · ml^{-1} for (+)-ASOX and 54.9 ng · ml^{-1} for (–)-ASOX) differed significantly between the ASOX enantiomers ($P \leq 0.05$; paired *t*-test). However, the t_{max} values obtained did not differ (2.4 vs 2.4 h). The area under the plasma concentration-time curve ($AUC_{SS}^{0–8}$) for (+)-ASOX was also significantly greater than that obtained for the other enantiomer (1719.2 vs 261.4 ng · h · ml^{-1}).

TABLE 2. Kinetic disposition of (+)-ASOX and (–)-ASOX. Data are reported as mean (95% CI) and median (n = 18)[†]

	(+)ASOX mean (95% CI) median	(–) ASOX mean (95% CI) median
C_{max} (ng · ml^{-1})	301.6 (179.7–423.5) 250.1	54.9* (21.9–87.9) 20.8
t_{max} (h)	2.4 (2.0–2.9) 2.0	2.4 (1.9–2.8) 2.0
$t_{1/2}f$ (h)	0.7 (0.5–1.0) 0.7	0.9 (0.6–1.1) 0.6
K_f (h^{-1})	1.2 (0.9–1.6) 1.1	1.4 (0.6–2.1) 0.8
$t_{1/2}$ (h)	5.2 (4.1–6.3) 4.7	3.3* (2.8–3.8) 3.3
K_{el} (h^{-1})	0.2 (0.1–0.2) 0.2	0.2* (0.2–0.3) 0.2
$AUC_{SS}^{0–8}$ (ng · h · ml^{-1})	1719.2 (978.6–2459.8) 1316.3	261.4* (102.9–419.8) 106.3
Cl/fm (l · h^{-1} · kg^{-1})	5.8 (3.8–7.8) 5.1	54.0* (35.2–72.7) 50.0
(+)/(–) $AUC_{SS}^{0–8}$	9.2 (7.6–10.9) 9.3	

[†]C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; $t_{1/2}f$, formation half-life; K_f = formation rate constant; $t_{1/2}$, elimination half-life; K_{el}, elimination rate constant; $AUC_{SS}^{0–8}$, area under the plasma concentration-time curve; Cl/fm, apparent clearance.
*$P < 0.05$ (paired *t*-test).

The data presented in Figure 2 show the high variability observed in the plasma concentrations of (+)-ASOX and (–)-ASOX. The low plasma concentrations of both ASOX enantiomers observed in some patients has been previously reported by Marriner et al. (1986),[8] Cotting et al. (1990),[10] and Takayanagui et al. (1997).[3] The mechanisms to the variability of albendazole sulfoxide plasma concentrations remains speculative. The influence of foods rich in fat in the systemic availability of albendazole was reported by Lange et al. (1988).[11] On the other hand, Sánches et al. (1996)[16] showed that the poor nutritional condition of the feed-restricted cattle increased the peak plasma concentrations and the plasma half-lives of both albendazole metabolites. The patients included in this investigation fasted for 12 h before and 3 h after drug administration.

The AUC_{SS}^{0-8} ratio (+)/(–) ranged from 7.6 to 10.9, with a mean of 9.2. Figure 3 presents the plasma concentration ratio (+)/(–) (means for the 18 patients investigated) observed at each sampling time during a period of 12 h after the administration of the last albendazole dose. The data demonstrate an increase in enantiomer ratio as a function of time, with the implication of preferential (–)-ASOX formation up to t_{max} and inversion of the enantiomer ratio during the elimination phase, with evidence of (+)-ASOX accumulation. The alterations observed in the enantiomer ratio as a function of time may be the consequence of enantioselectivity in the sulfonation reaction depending on the cytochome P450 system. This interpretation assumes that the selective consumption of (–)-ASOX in ASON formation is responsible for the accumulation of (+)-ASOX in plasma.[12,14] These data demonstrate enantioselectivity both in the phase of ASOX formation and elimination. Delatour et al. (1991a)[12] observed enantiomer ratios of up to 13.1 during the investigation of 4 healthy male volunteers treated with a single dose of albendazole.

Moroni et al. (1995)[6] reported that enantioselectivity in albendazole sulfoxidation in rat liver microsomes depends on two enzyme systems, i.e., flavin mono-oxygenase (FMO) and the cytochrome P450 system (CYP). The involvement of FMO results in the formation of (+)-ASOX predominantly whereas CYP2C6 and/or CYP2A1 preferentially produce (–)-ASOX and CYP3A catalyses the formation of racemic ASOX. Thus, in albendazole sulfoxidation, the enantioselectivity of FMO is the reverse of that of the CYPs. The metabolism of albendazole to ASOX in human liver microsomes also involves both enzyme systems, i.e., FMO and the CYPs.[18]

In view of the above considerations, drug interactions may result in different plasma concentration ratios ((+)/(–)) of ASOX enantiomers.

Treatment of rats with dexamethasone results in the induction of CYP3A1 and a consequent increase in sulfoxi-

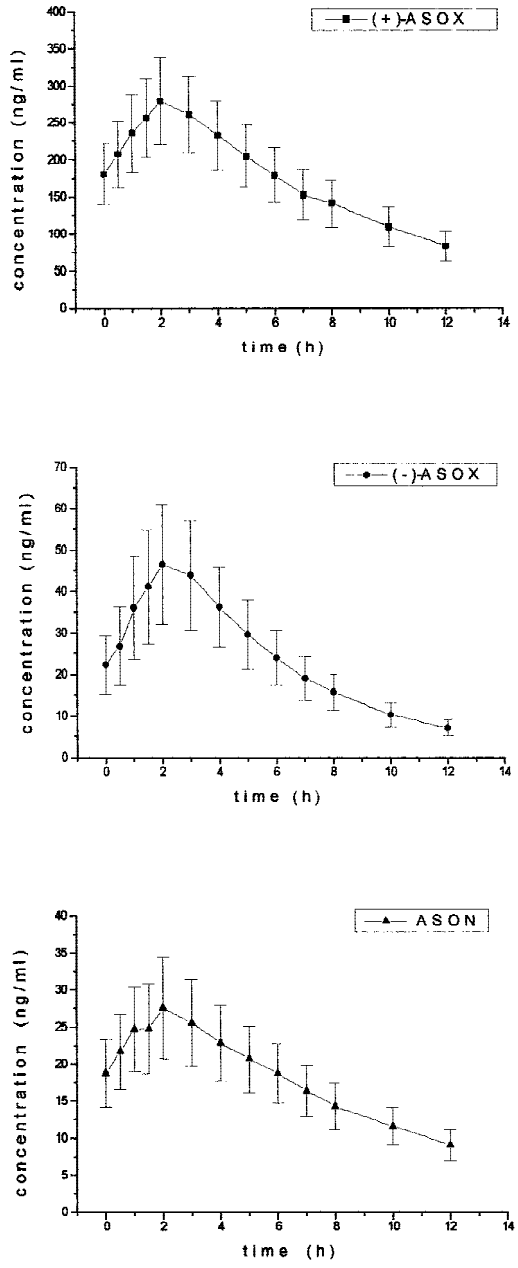

Fig. 2. Plasma concentration-time curve of (+)-ASOX, (–)-ASOX and ASON. Data are reported as mean ± SEM (n = 18).

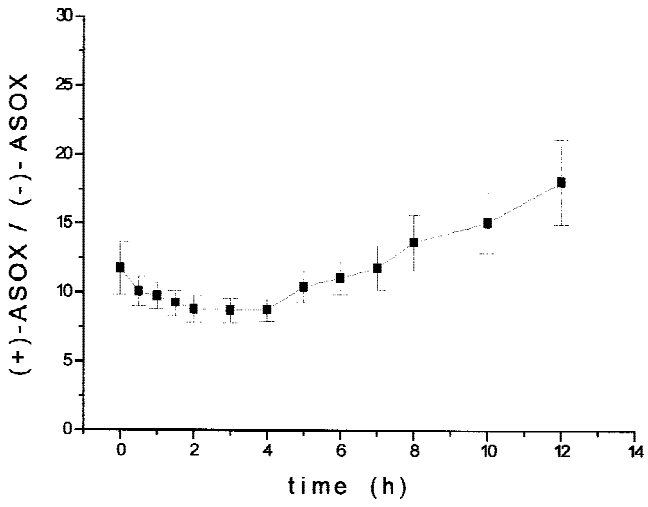

Fig. 3. Plasma concentration ratio ((+)/(–)) of ASOX. Data are reported as mean ± SEM (n = 18).

dation.[6] Takayanagui et al. (1997)[3] reported significantly higher plasma ASOX concentrations in patients with neurocysticercosis simultaneously treated with albendazole and dexamethasone with and without cimetidine. The authors observed a reduction of ASOX clearance and a prolongation of its elimination half-life.

Some patients (8 of 18) included in the present investigation received dexamethasone during treatment with albendazole because of the acute inflammatory reaction caused by the death of the cysticercus. There were no significant differences in the pharmacokinetic parameters describing (+)-ASOX and (–)-ASOX in patients concomitantly treated (dexamethasone group) or not (control group) with dexamethasone. Both dexamethasone and carbamazepine are inducers of CYP3A, the enzymes involved in the formation of racemic ASOX in rats.[3,6,19] The inclusion of a larger number of patients treated with carbamazepine in the control group (n = 4) than in the dexamethasone group (n = 2) may explain the lack of interaction between albendazole and dexamethasone in the population investigated.

Some of the present patients also received phenytoin during the treatment of neurocysticercosis with albendazole. Considering the absence of clinical data about the effects of antiepileptic drugs on ASOX pharmacokinetics, the induction of specific forms of CYP is only a matter of speculation. There is no report of the induction of CYP2C6 and CYP2A1 involved in the enantioselective formation of ASOX or of CYP1A involved in sulfoxidation in rats.[6] Although the interaction with antiepileptic drugs probably does not alter the enantiomer ratio of ASOX, clinical studies on the interaction of ASOX with antiepileptic drugs are needed because of their frequent combination during treatment of neurocysticercosis.

The Cl/fm for ASOX expressed as mean ranged from 5.8 $l \cdot h^{-1} \cdot kg^{-1}$ ((+)-ASOX) to 54.0 $l \cdot h^{-1} \cdot kg^{-1}$ ((–)-ASOX), $P \leq 0.05$, characterizing an increase of a 932% for (–)-ASOX and compatible with the higher plasma concentrations observed for (+)-ASOX. The elimination half-life of ASOX ranged from 4.1 to 6.3 h for (+)-ASOX and from 2.8 to 3.8 h for (–)-ASOX (Table 2). The significantly more prolonged elimination half-life for (+)-ASOX is compatible with the higher plasma concentrations observed for this enantiomer. The elimination half-life values for both enantiomers were lower than those reported by Cotting et al. (1990)[10] and Jung et al. (1992)[9] in studies on the use of a single dose of albendazole. The data obtained in the present study in which albendazole was administered in multiple doses (5 mg/kg every 8 h) are consistent with the autoinduction of the form(s) of CYP involved in albendazole metabolism.[20,21] Albendazole sulfone is an inactive metabolite formed in a P450-mediated liver microsomal sulfonation reaction. Its disposition may be rate limited by the disposition of ASOX. The pharmacokinetic parameters of ASON are summarized in Table 3. The elimination half-life of 5.8 h was close to the value of 5.2 h obtained for (+)-ASOX. Furthermore, the apparent clearance (Cl/fm) of ASOX of 60.3 $l \cdot h^{-1} \cdot kg^{-1}$ was similar to that observed for (–)-ASOX, a mean value of 54.0 $l \cdot h^{-1} \cdot kg^{-1}$ (Table 2). These data are consistent with the plasma accumulation of (+)-ASOX due to the higher elimination rate of (–)-ASOX, confirming the dependence of the kinetic disposition of ASON on the intermediate metabolite ASOX. The sulfone formation capacity, defined as the ratio $AUC_{SS}{}^{0-8}{}_{ASON}/AUC_{SS}{}^{0-8}{}_{ASOX} + AUC_{SS}{}^{0-8}{}_{ASON}$ was 8.0 (7.0–8.9) expressed as mean (Cl 95%) for the population investigated. The plasma ASON/ASOX concentration ratios were practically constant over a 12-h period of collection, as indicated by data presented in Figure 4.

TABLE 3. Kinetic disposition of the ASON. Data are reported as mean (95% Cl) and median (n = 18)*

	ASON mean (95% Cl) median
C_{max} ($ng \cdot ml^{-1}$)	31.1 (16.7–45.4) 21.9
t_{max} (h)	2.3 (1.7–2.8) 2.0
$t_{1/2}f$ (h)	0.6 (0.4–0.8) 0.5
K_f (h^{-1})	2.0 (1.2–2.9) 1.4
$t_{1/2}$ (h)	5.8 (4.9–6.8) 5.4
K_{el} (h^{-1})	0.1 (0.1–0.2) 0.1
$AUC_{SS}{}^{0-8}$ ($ng \cdot h \cdot ml^{-1}$)	176.2 (94.4–258.0) 122.8
Cl/fm ($l \cdot h^{-1} \cdot kg^{-1}$)	60.3 (39.1–81.6) 54.9
$AUC_{SS}{}^{0-8}{}_{ASON}/AUC_{SS}{}^{0-8}{}_{ASOX} + AUC_{SS}{}^{0-8}{}_{ASON}$	8.0 (7.0–8.9) 7.9

*ASON, albendazole sulfone; C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; $t_{1/2}f$, formation half-life; K_f = formation rate constant; $t_{1/2}$, elimination half-life; K_{el}, elimination rate constant; $AUC_{SS}{}^{0-8}$, area under the plasma concentration-time curve; Cl/fm, apparent clearance.

The data reported for the 18 patients investigated dem-

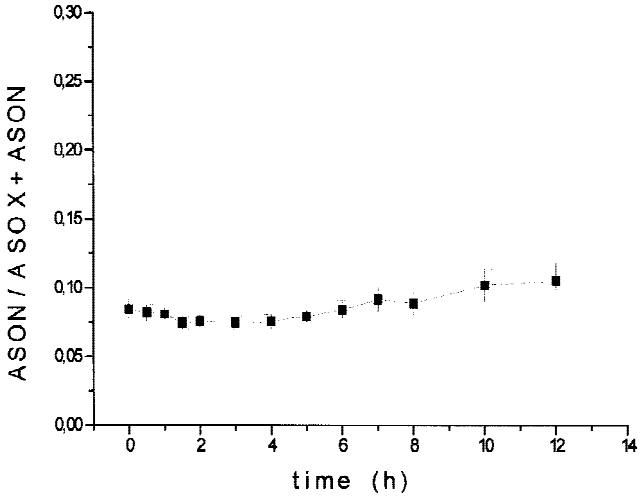

Fig. 4. Plasma concentration ratio ASON/ASOX + ASON during a period of 12 h after albendazole administration. Data are expressed as mean ± SEM (n = 18).

onstrate enantioselectivity in albendazole metabolism, with accumulation of the (+)-ASOX enantiomer. However, there are no data in the literature about the selectivity or exclusivity of this enantiomer in the expression of the systemic biological activity required in the treatment of neurocysticercosis.

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