Enantioselective Renal Excretion of Albendazole Metabolites in Patients With Neurocysticercosis

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ABSTRACT The present study investigates the urinary excretion of the enantiomers of (+)- and (−)-albendazole sulfoxide (ASOX) and albendazole sulfone (ASON) in 12 patients with neurocysticercosis treated with albendazole for 8 days (7.5 mg/kg/12 h). Serial blood samples (0–12 h) and urine (three periods of 8 h) were collected after administration of the last dose of albendazole. Plasma and urine (+)-ASOX, (−)-ASOX, and ASON metabolites were determined by HPLC using a chiral phase column (Chiralpak AD) with fluorescence detection. The pharmacokinetic parameters ($P < 0.05$) for (+)-ASOX, (−)-ASOX, and ASON metabolites are reported as means (95% CI); amount excreted (Ae) = 3.19 (1.53–4.85) vs. 0.72 (0.41–1.04) vs. 0.08 (0.03–0.13) mg; plasma concentration-time area under the curve, AUC^{0-24} = 3.56 (0.93–6.18) vs. 0.60 (0.12–1.08) vs. 0.38 (0.20–0.55) μg.h/ml, and renal clearance Cl_R = 1.20 (0.66–1.73) vs. 2.72 (0.39–5.05) vs. 0.25 (0.13–0.37) l/h. Sulfone formation capacity, expressed as the Ae ratio ASON/ASOX + ASON, was 2.21 (1.43–2.99). These data point to enantioselectivity in the renal excretion of ASOX as a complementary mechanism to the metabolism responsible for the plasma accumulation of (+)-ASOX. The results also suggest that the metabolite ASON is partially eliminated as a reaction product of the subsequent metabolism. *Chirality 16:520–525, 2004.*

KEY WORDS: albendazole; metabolism; renal excretion; enantiomers; neurocysticercosis; pharmacokinetics

Albendazole (methyl 5-propylthio-1H-benzimidazol-2-yl carbamate) is a broad-spectrum anthelmintic drug which is active against gastrointestinal nematodes and the larval stages of cestodes such as *Echinococcus granulosus* and *Taenia solium*. Albendazole has been used in clinical practice for the treatment of neurocysticercosis since 1987. Administration of albendazole for 8 days during the treatment of human intraparenchymatous neurocysticercosis results in the elimination of 80–85% of the cysticerci. Adverse reactions during the first days of treatment such as headaches and exacerbation of neurological symptoms due to acute inflammation secondary to the sudden destruction of cysticerci are minimized or eliminated by corticosteroid therapy.[1,2]

Albendazole is characterized by high presystemic elimination and is of unknown bioavailability. The two main metabolites, albendazole sulfoxide (ASOX) and albendazole sulfone (ASON), are produced by S-oxidation (Fig. 1). ASOX is the metabolite responsible for both the efficacy and toxicity of albendazole. The formation of ASOX depends on flavin monooxygenases (FMO) and the cytochrome P450 system (CYP), mainly CYP3A4 and, to a lesser extent, CYP1A2. The biotransformation of ASOX to the inactive metabolite ASON depends on as yet unidentified CYP isoform(s).[3–5]

S-oxidation of albendazole introduces a chiral center with the production of (+)- and (−)-ASOX.[6,7] However, no data are available about the absolute configuration or biological activity of the isolated enantiomers. The kinetic disposition of the chiral metabolite is enantioselective, with plasma accumulation of the (+) enantiomer such that (+)/(−) ratios ranging from 7 to 9 are seen in patients treated with multiple doses of albendazole.[8] (+)/(−) Ratios different from 1 can therefore only be explained by the enantioselective metabolism and/or disposition of albendazole. Moroni et al.[6] observed enantioselectivity in the in vitro sulfoxidation of albendazole in rat liver microsomes. The authors reported that FMO-dependent S-oxidation results in the predominant formation of (+)-ASOX, while CYP2C6 and/or CYP2A1 favor the production of the (−) enantiomer and CYP3A produces equivalent amounts of both enantiomers. The relative contribution of CYP and FMO to the sulfoxidation of albendazole varies according

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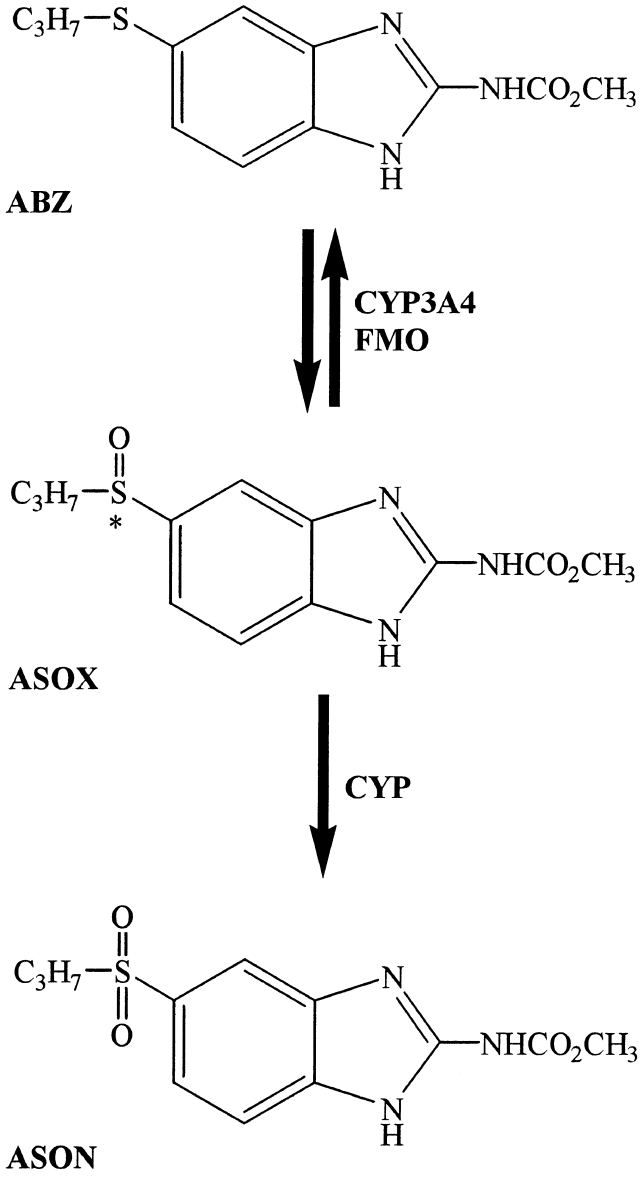

Fig. 1. Albendazole metabolism. The asterisk indicates the chiral center generated during the sulfoxidation of albendazole.

to the animal species studied, and thus explains the differences in the (+)/(−) ratios observed among species.[7,9,10] Rawden et al.[3] reported that in human liver microsomes CYPs contribute more to albendazole sulfoxidation than FMO does (70% vs. 30%).

Clinical studies on the kinetic disposition of albendazole employing nonenantioselective assays are only based on plasma[7,8,11–15] and cerebrospinal fluid[16] concentration data. Analytical methods capable of chiral discrimination are also restricted to the plasma and cerebrospinal fluid matrices.[17–21] Renal excretion of ASOX has only been studied by Marriner et al.[22] in healthy volunteers and by Sánchez et al.[23] in patients with neurocysticercosis treated with albendazole. Both groups reported only the nonenantioselective renal clearance rates of ASOX, with values ranging from 0.2–0.8 l/h for healthy volunteers and from 0.01–0.04 l/kg/h for patients with neurocysticercosis.

The aim of the present study was to determine the enantioselectivity of renal ASOX excretion and its possible contribution to the plasma accumulation of the (+) enantiomer in patients with neurocysticercosis receiving albendazole in a multiple dose regimen, as well as to assess renal excretion of the metabolite ASON.

PATIENTS AND METHODS

Patients

The study was conducted in 12 nonobese (51–89.4 kg) patients (five men, seven women), ages 25–50 years, with the active form of intraparenchymatous neurocysticercosis (diagnosed by computer assisted tomography and/or magnetic resonance imaging, and ELISA for cysticercosis in cerebrospinal fluid) and whose hepatic and renal functions were normal (Table 1). The clinical protocol was approved by the Research Ethics Committee of the Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. The patients were admitted to the hospital and received albendazole (Zentel, tablets; SmithKline Beecham Laboratórios, Rio de Janeiro, RJ) in a multiple dose regimen (7.5 mg/kg every 12 h) for 8 days. On the eighth day, after administration of the last albendazole dose, blood was collected with heparinized syringes (Liquemine, 5000 IU, Roche, Nutley, NJ) at time zero, and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 h; urine was obtained over three consecutive periods of 8 h. Plasma obtained by centrifugation at 1,800*g* for 20 min was stored at −20°C prior to analysis. The 8-h urine volume was determined and an aliquot was removed and stored at −20°C until analyzed.

Albendazole Metabolites in Plasma Samples

Albendazole metabolite concentrations in plasma samples were determined as described by Lanchote et al.[17] Briefly, the drugs were extracted from 500 μl plasma with ethyl acetate and the resolution of ASOX enantiomers and ASON was achieved on a Chiralpak AD column using hexane-isopropanol-ethanol (81:14.25:4.75, v/v/v) as mobile phase. The compounds were detected by fluorescence (λ_{exc} 280 nm, λ_{em} 320 nm). Linear standard curves were obtained in the concentration range of 5–2,500 ng/ml for the ASOX enantiomers and 1–500 ng/ml for ASON. The method is precise and accurate for the three compounds, as judged by the coefficients of variation and relative errors lower than 10%.

Albendazole Metabolites in Urine Samples

Standard solutions and reagents. The stock solutions of racemic ASOX (99.4%, Robert Young & Co., Glasgow, UK) and ASON (99.8%, Robert Young) were prepared in methanol at concentrations of 1.0 and 0.1 mg/ml, respectively. The solutions were diluted in methanol at concentrations of 50.0, 20.0, 10.0, 2.0, and 1.0 μg of each ASOX enantiomer/ml and at concentrations of 10.0, 4.0, 0.8, 0.4, and 0.2 μg of ASON/ml. The solutions were stored at −20°C and remained stable for 3 months.

TABLE 1. Individual characteristics of the investigated patients (n = 12)

Patient	Sex	Age (years)	Weight (kg)	Combined drugs
1	F	40	67.0	amitriptyline, diazepam
2	M	44	89.4	clobazam, dexamethasone, phenobarbital
3	M	46	77.0	phenobarbital
4	F	25	52.0	dexamethasone, phenytoin, ranitidine
5	F	40	59.5	dexamethasone, phenytoin, ranitidine
6	F	38	57.5	carbamazepine, clobazam
7	M	30	73.2	carbamazepine, metoclopramide, ranitidine
8	F	43	78.0	—
9	F	38	60.5	phenobarbital
10	M	27	67.0	—
11	F	23	51.0	ranitidine, bromocriptine, propranolol, levodopa, benzamide
12	M	50	76.7	—

Sodium metabisulfite solution (analytical grade; Merck, Darmstadt, Germany) was prepared in water at a concentration of 4 mg/ml. The solvents used for the extraction procedure and for chromatographic analysis were of HPLC grade (Mallinckrodt ChromAR, Paris, KY).

Extraction procedure. Urine samples (100 μl) were added to 50 μl of the sodium metabisulfite solution and 100 μl 0.75 N acetate buffer, pH 7.0, and extracted with 5.0 ml dichloromethane for 1 min in a mixer. After centrifugation at 1,800*g* for 5 min and separation of the organic phases (4.0 ml), the extracts were evaporated dry under air flow. The residues were dissolved in 200 μl of the mobile phase and submitted to chromatographic analysis (50 μl).

Chromatographic analysis. The HPLC system consisted of a Shimadzu chromatograph equipped with an LC-10 AS pump, an FR 551 fluorescence detector (λ_{exc} = 280 nm, λ_{em} = 320 nm), a CR 6A integrator, and a model 7125 Rheodyne injector (50-μl sampler). The albendazole metabolites were separated on a 250 × 4 mm Chiralpak AD chiral phase column (Chiral Technologies, Exton, PA) containing 10-μm particles, equipped with a 4 × 4 mm CN Lichrospher 100 (Merck) precolumn 10-μm particle size, with the mobile phase consisting of n-hexane/isopropanol/ethanol (81:14.75:4.25, v/v/v), at a flow rate of 1.1 ml/min.

Confidence limits. The calibration curves were constructed by duplicate analysis of 100-μl aliquots of blank urine (obtained from volunteers who did not receive any medication during the last 72 h) enriched with 25 μl of each of the albendazole metabolite standard solutions (0.25–12.5 μg of each ASOX enantiomer/ml urine and 0.05–2.5 μg ASON/ml urine). The samples were submitted to the extraction procedure and chromatographic analysis as described above. The linear regression equations and correlation coefficients were calculated from the height of the peaks plotted against the respective urine concentrations.

Recovery, quantification limit, linearity, and precision were calculated using blank urine samples spiked with standard solutions of the albendazole metabolites. Recovery of the metabolites was calculated by analyzing urine samples spiked with the standard ASOX and ASON solutions, based on calibration curves from the standard metabolite solutions not submitted to the extraction procedure. Recovery was determined at concentrations of 0.25, 1.0, and 12.5 μg of (+)-ASOX, (−)-ASOX, and ASON/ml urine. The quantification limit was defined as the lowest intraday concentration of each metabolite analyzed, with a coefficient of variation of less than 15%. Linearity was determined up to a concentration of 100 μg of each ASOX enantiomer/ml urine and up to 10 μg of ASON/ml urine. Intra- and interday precision was determined at three concentrations of each metabolite (0.25, 1.0, and 12.5 μg /ml urine) and the results are reported as intra- and interday coefficients of variation. Intraday precision was calculated by analyzing five aliquots of each spiked sample based on a single calibration curve. The other aliquots of the same sample were analyzed on 5 different days for the determination of interday precision. Selectivity of the method was evaluated by directly injecting drugs commonly used in combination with albendazole during neurocysticercosis treatment.

Pharmacokinetic and Statistical Analysis

The steady-state plasma concentration vs. time area under the curve during the period from time zero to 12 h (AUC^{0-12}) of each albendazole metabolite was estimated by the trapezoidal method. The remaining area for the period from 12–24 h was obtained by extrapolation of the plasma concentration vs. time log curve. The amount of each albendazole metabolite excreted in urine (Ae) during the three 8-h intervals was determined by multiplying the urine concentration by the corresponding urine volume. The amount excreted in 0–24-h urine was obtained by summing the values of the three 8-h periods. Renal clearance of each metabolite was calculated based on urinary excretion (Ae) and plasma concentration during the same time interval t, using the following equation: $CL_R = Ae^{0-24}/AUC^{0-24}$. The log curve of the urinary excretion rate ($\Delta xu / \Delta t$) vs. midpoint time (t_{mp}) permitted determination of the elimination half-life of the metabolite (t1/2),

with the consequent calculation of the elimination rate constant (Kel) using the Kel = 0.693/t1/2 equation.[8,22,23]

The results are expressed as the mean (95% CI). Differences among (+)-ASOX, (−)-ASOX, and ASON were analyzed by one-way analysis of variance (ANOVA) followed by the Tukey-Kramer multiple comparisons test, accepting $P < 0.05$ as significant.

RESULTS AND DISCUSSION

Clinical studies on the enantioselective kinetic disposition of the active metabolite of ASOX are restricted to data on plasma and cerebrospinal fluid concentrations. Delatour et al.[7] observed (+)/(−) ratios of up to 13.1 in a study on four healthy volunteers treated with a single dose of albendazole. Marques et al.,[8] studying 18 patients with intraparenchymatous neurocysticercosis treated with albendazole for 8 days, reported ratios of 7.6 to 10.9. The authors suggested that the enantioselective formation of ASOX and the possibility of the selective consumption of (−)-ASOX during sulfonation, with the consequent plasma accumulation of the (+)-ASOX. No clinical studies on the enantioselective renal excretion of ASOX are reported in the literature.

The present investigation was conducted on 12 adult patients treated with albendazole (7.5 mg/kg/12 h) for 8 days. Urine was collected during the last 12-h interval up to 24 h after albendazole administration. Seven of the 12 patients studied had received carbamazepine, phenytoin, or phenobarbital for the control of epileptic seizures for at least 3 months prior to the study (Table 1). Lanchote et al.[15] reported that phenytoin, carbamazepine, and phenobarbital induce, to approximately the same extent, the oxidative metabolism of albendazole in a nonenantioselective manner. Three of the 12 patients received dexamethasone (Table 1) to decrease neurological symptoms due to the death of the parasite, but it does not alter the (+)/(−) enantiomeric ratio of the ASOX metabolite in patients with neurocysticercosis.[8]

The method developed for analysis of the ASOX enantiomers and ASON in urine is slightly modified from that used for the determination of the metabolites in plasma by Lanchote et al.[17]

The metabolites were eluted from a Chiralpak AD chiral phase column in the order (+)- and (−)-ASOX and ASON over ~30 min. The elution order was established previously by Lanchote et al.[17] Urine extraction with dichloromethane at pH 7.0 resulted in chromatograms which were free of interfering compounds, and in recoveries of ~90% for both ASOX enantiomers and ~95% for ASON. It should be noted that drugs normally used in combination with albendazole, such as dexamethasone, phenobarbital, carbamazepine, phenytoin, cimetidine, and ranitidine, did not interfere with the analytic method due to the high selectivity of fluorescence detection. The quantification limit of 150 ng/ml urine for each ASOX enantiomer and of 30 ng/ml urine for ASON permits the application of the method to clinical studies employing multiple dose regimens of albendazole. The linearity of the method was evaluated over concentration ranges of 0.15–100 μg/ml for both ASOX enantiomers and 0.03–10 μg/ml for ASON. The regression lines were linear over the concentrations examined and the

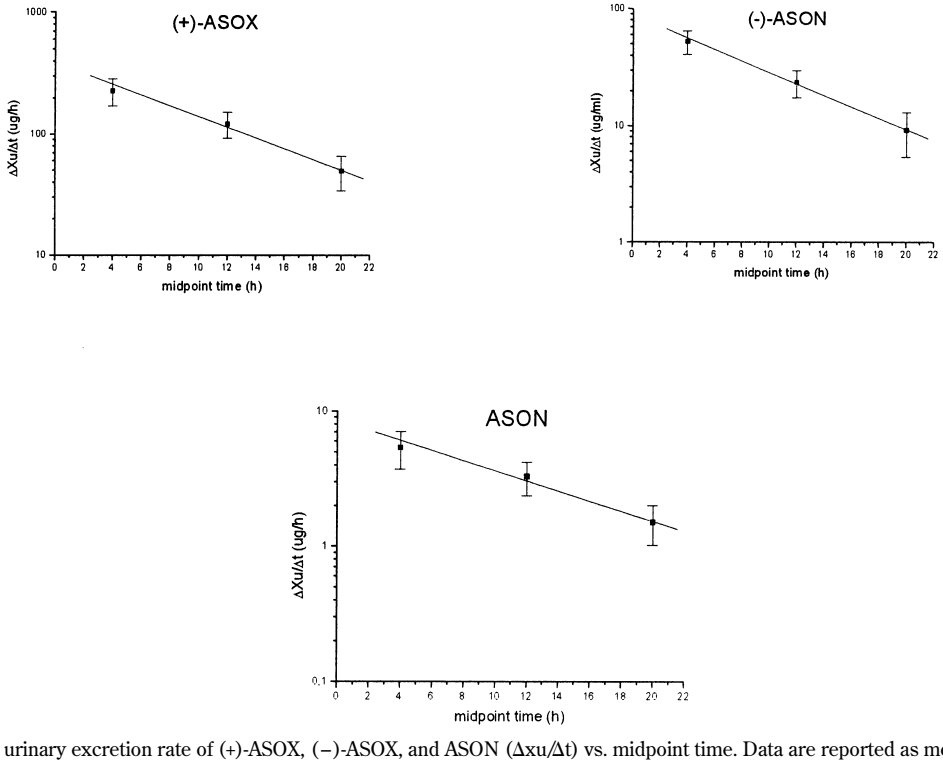

Fig. 2. Plots of log urinary excretion rate of (+)-ASOX, (−)-ASOX, and ASON (Δxu/Δt) vs. midpoint time. Data are reported as means ± SEM (n = 12).

TABLE 2. Kinetic disposition of albendazole metabolites in urine

	(+)-ASOX	(−)-ASOX	ASON
t1/2 (h)	6.59 (5.04–8.14)	7.04 (4.68–9.40)	7.68 (6.05–9.32)
Ae (mg)	3.19 (1.53–4.85)	0.72* (0.41–1.04)	0.08** (0.03–0.13)
AUC^{0-24} (μg.h/ml)	3.56 (0.93–6.18)	0.60* (0.12–1.08)	0.38** (0.20–0.55)
Cl_R ($1.h^{-1}$)	1.20 (0.66–1.73)	2.72* (0.39–5.05)	0.25*** (0.13–0.37)
$Ae_{(+)\text{-ASOX}}$ / $Ae_{(-)\text{-ASOX}}$	5.17 (3.28–7.07)		
Ae_{ASON} / $Ae_{ASOX+ASON}$ Sulfonation (%)		2.21 (1.43–2.99)	

Data reported as mean (95% CI).
$P < 0.05$ Tukey-Kramer multiple comparisons test: *(+)–ASOX vs. (−)-ASOX; **(+)-ASOX vs. ASON; ***(−)-ASOX vs. ASON.
t1/2, elimination half-life; Kel, elimination rate constant; Ae, amount excreted; AUC, plasma concentration-time area under curve; Cl_R, renal clearance.

correlation coefficients of the calibration curves ranged from 0.9838–0.9969. The coefficients of variation of less than 7.5% obtained for the intra- and interday precision ensured the reproducibility of the method for the analysis of small urine volumes of 100 μl. We conclude that the method developed for the sequential analysis of albendazole metabolites in urine is simple, sensitive, selective, and reproducible.

The possible use of an internal standard was explored during the development of the method. Unfortunately, the selective conditions needed for fluorescence detection made the search unsuccessful. However, the observed precision gave a reliable method.

The elimination half-life of the albendazole metabolites determined based plots of the log urinary excretion rate as a function of the midpoint time was on average 7 h for (+)-ASOX, (−)-ASOX, and ASON (Fig. 2; Table 2). Marques et al.,[8] studying patients with neurocysticercosis treated with antiepileptics, reported mean elimination half-lives calculated from the plasma concentration vs. time curves of 5 h for (+)-ASOX, 3 h for (−)-ASOX, and 6 h for ASON.

The amount of (+)-ASOX excreted over 24 h was ~5 times higher than the excreted amount of (−)-ASOX (Table 2). The (+)/(−) plasma concentration ratio (AUC^{0-24}) was close to 6 for the same patients, suggesting that the plasma accumulation of the (+) enantiomer is not only a consequence of the enantioselective metabolism, but also of the higher rate of renal excretion of its (−) antipode. This mechanism is compatible with the higher renal clearance observed for (−)-ASOX compared to (+)-ASOX (2.72 vs. 1.20 l/h).

Sánchez et al.[23] estimated the renal clearance of ASOX in patients treated with albendazole as a multiple dose regimen, but did not employ enantioselective methods for the plasma and urine metabolite concentrations. The reported renal clearance rates, the sum of both enantiomers, were 0.01 to 0.04 l/kg/h, thus being on the same order of those obtained in the present study.

Renal excretion of ASON has not been reported in the literature. The renal clearance of 0.25 l/h obtained for ASON did not differ from that observed for (+)-ASOX, but was ~10 times lower than the renal clearance of (−)-ASOX (0.25 vs. 2.72 l/h) (Table 2). The 2.2% sulfonation observed in urine of the 12 patients studied (Table 2) was lower than the 7–9% sulfonation calculated from plasma concentration data,[8] suggesting that the ASON metabolite is partially eliminated after further metabolism.

The present results demonstrate the enantioselectivity in the renal clearance of ASOX, favoring (−)-ASOX. Enantioselective renal excretion may be considered to be a complementary mechanism to metabolism in explaining the plasma accumulation of (+)-ASOX.

LITERATURE CITED

1. Takayanagui OM. Therapy for neurocysticercosis. Expert Rev Neurother 2004;4:129–139.
2. Garcia HH, Evans CAW, Nash TE, Takayanagui OM, White AC, Botero D, Rajshekhar V, Tsang VCW, Schantz PM, Allan JC, Flisser A, Correa D, Sarti E, Friedland JS, Martinez SM, Gonzalez AE, Gilman RH, Del Brutto OH. Current consensus guidelines for treatment of neurocysticercosis. Clin Microbiol Rev 2002;15:747–756.
3. Rawden HC, Kokwaro GO, Ward SA, Edwards G. Relative contribution of cytochromes P-450 and flavin-containing monoxygenases to the metabolism of albendazole by human liver microsomes. Br J Clin Pharmacol 2000;49:313–322.
4. Souhaili-El Amri H, Mothe O, Totis M, Masson C, Batt AM, Delatour P, Siest G. Albendazole sulfonation by rat liver cytochrome P-450c. J Pharmacol Exp Ther 1988;246:758–764.
5. Villaverde C, Alvarez AI, Redondo P, Voces J, Del Estal JL, Prieto JG. Small intestinal sulphoxidation of albendazole. Xenobiotica 1995;25:433–441.
6. Moroni P, Buronfosse T, Longin-Sauvageon C, Delatour P, Benoit E. Chiral sulfoxidation of albendazole by the flavin adenine dinucleotide-containing and cytochrome P450-dependent monoxygenases from rat liver microsomes. Drug Metab Dispos 1995;23:160–164.
7. Delatour P, Benoit E, Besse S, Boukraa A. Comparative enantioselectivity in the sulphoxidation of albendazole in man, dogs and rats. Xenobiotica 1991;21:217–221.
8. Marques MP, Takayanagui OM, Bonato PS, Santos SRCJ, Lanchote VL. Enantioselective kinetic disposition of albendazole sulfoxide in patients with neurocysticercosis. Chirality 1999;11:218–223.
9. Delatour P, Benoit E, Caude M, Tambute A. Species differences in the generation of the chiral sulfoxide metabolite of albendazole in sheep and rats. Chirality 1990;2:156–160.
10. Delatour P, Garnier F, Benoit E, Caude I. Chiral behaviour of the metabolite albendazole sulphoxide in sheep, goats and cattle. Res Vet Sci 1991;50:134–138.
11. Cotting J, Zeugin T, Steiger U, Reichen J. Albendazole kinetics in patients with echinococcosis: delayed absorption and impaired elimination in cholestasis. Eur J Clin Pharmacol 1990;38:605–608.
12. Lange H, Eggers R, Bircher J. Increased systemic availability of albendazole when taken with a fatty meal. Eur J Clin Pharmacol 1988;34:315–317.
13. Jung H, Hurtado M, Sanchez M, Medina MT, Sotelo J. Clinical phar-

macokinetics of albendazole in patients with brain cysticercosis. J Clin Pharmacol 1992;32:28–31.

14. Takayanagui OM, Lanchote VL, Marques MPC, Bonato PS. Therapy for neurocysticercosis: pharmacokinetic interaction of albendazole sulfoxide with dexamethasone. Ther Drug Monit 1997;19:51–55.
15. Lanchote VL, Garcia FS, Dreossi SAC, Takayanagui OM. Pharmacokinetic interaction between albendazole sulfoxide enantiomers and antiepileptic drugs in patients with neurocysticercosis. Ther Drug Monit 2002;24:338–345.
16. Takayanagui OM, Bonato PS, Dreossi SAC, Lanchote VL. Enantioselective distribution of albendazole metabolites in cerebrospinal fluid of patients with neurocysticercosis. Br J Clin Pharmacol 2002;54: 125–130.
17. Lanchote VL, Marques MPC, Takayanagui OM, Carvalho R, Bonato PS. Simultaneous determination of albendazole sulfoxide enantiomers and albendazole sulfone in plasma. J Chromatogr B 1998;709: 273–279.
18. Garcia JJ, Bolás-Fernández F, Torrado JJ. Quantitative determination of albendazole and its main metabolites in plasma. J Chromatogr B 1999;723:265–271.
19. Kitzman D, Cheng KJ, Fleckenstein L. HPLC assay for albendazole and metabolites in human plasma for clinical pharmacokinetic studies. J Pharm Biomed Anal 2002;30:801–813.
20. Paias FO, Lanchote VL, Takayanagui OM, Bonato PS. Enantioselective analysis of albendazole sulfoxide in cerebrospinal fluid by capillary electrophoresis. Electrophoresis 2001;22:3263–3269.
21. Bonato PS, Lanchote VL, Takayanagui OM. Simultaneous liquid chromatography-tandem mass spectrometric determination of albendazole sulfoxide and albendazole sulfone in plasma. J Chromatogr B 2003;783:237–245.
22. Marriner SE, Morris DL, Dickson B, Bogan JA. Pharmacokinetics of albendazole in man. Eur J Clin Pharmacol 1986;30:705–708.
23. Sánches M, Suástegui R, Gonzáles-Esquivel D, Sotelo J, Jung H. Pharmacokinetic comparison of two albendazole dosage regimens in patients with neurocysticercosis. Clin Neuropharmacol 1993;16: 77–82.