Therapeutic Drug Monitoring
24:338–345 © 2002 Lippincott Williams & Wilkins, Inc., Philadelphia

Pharmacokinetic Interaction Between Albendazole Sulfoxide Enantiomers and Antiepileptic Drugs in Patients With Neurocysticercosis

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Summary: The aim of the present investigation was to determine the interaction between the antiepileptic drugs (AEDs) phenytoin, carbamazepine, and phenobarbital and the enantioselective metabolism of albendazole. Thirty-two adults with a diagnosis of the active form of intraparenchymatous neurocysticercosis and treated with albendazole at the dose of 7.5 mg/kg every 12 hours for 8 days were studied. The patients were divided into four groups based on the combined use of AEDs or not: control group (n = 9), phenytoin group (n = 9 patients treated with 3–4 mg/kg/d sodium phenytoin), carbamazepine group (n = 9 patients treated with 10–20 mg/kg/d carbamazepine), and phenobarbital group (n = 5 patients treated with 1.5–4.5 mg/kg/d phenobarbital). Serial blood collections were carried out on day 8 of albendazole treatment during the last 12-hour dose interval. Plasma concentrations of the (+)- and (-)-albendazole sulfoxide (ASOX) and albendazole sulfone (ASON) metabolites were determined by high-performance liquid chromatography using a chiral phase column and fluorescence detection. The pharmacokinetic parameters were analyzed by analysis of variance followed by the Tukey-Kramer test. The results are reported as means. The following differences ($P < 0.05$) were observed between the control and the phenytoin, carbamazepine, and phenobarbital groups, respectively: (+)-ASOX area under the concentration–time curve for 0 to 12 hours after treatment (AUC^{0-12}) 6.1, 2.1, 3.1, 2.4 μg/h/mL; (+)-ASOX maximum plasma concentration (C_{max}) 0.8, 0.3, 0.4, 0.3 μg/mL; (+)-ASOX half-life ($t_{1/2}$) 8.0, 3.8, 4.1, 4.9 h; (-)-ASOX AUC^{0-12} 1.8, 0.4, 0.6, 0.5 μg/h/mL; (-)-ASOX C_{max} 0.2, 0.06, 0.1, 0.1 μg/mL; (-)-ASOX $t_{1/2}$ 4.3, 1.9, 2.2, 2.1 h; ASON AUC^{0-12} 0.5, 0.2 μg/h/mL; ASON C_{max} 0.8, 0.3, 0.4, 0.3 μg/mL; ASON $t_{1/2}$ 8.0, 3.8, 4.1 h. The results show that phenytoin, carbamazepine, and phenobarbital induce to approximately the same extent the oxidative metabolism of albendazole in a nonenantioselective manner. Notably, a significant reduction in the plasma concentration of the active ASOX metabolite was observed in patients with neurocysticercosis treated with these AEDs. **Key Words:** Albendazole—Antiepileptic drugs—Drug interactions—Neurocysticercosis—Pharmacokinetics.

Albendazole has been used for the pharmacologic treatment of neurocysticercosis since 1987. Epileptic convulsive seizures represent the main neurologic manifestation of neurocysticercosis and are considered to be one criterion for the evaluation of the disease in patients living in or returning from endemic regions. Consequently, the combined use of antiepileptic drugs (AEDs) is a relevant factor before and during albendazole treatment (1–5).

Few studies on the effects of albendazole on human cells are available; however, short-term administration of albendazole does not have severe side effects. Oral administration of albendazole results in low plasma

Received July 24, 2001; accepted November 13, 2001.

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concentrations of the unaltered drug (<10 ng/mL) due to its low absorption rate (low solubility in aqueous solutions, <1 μg/mL water, pH 7.4) and high presystemic elimination in the liver and gastrointestinal tract (5–9).

Albendazole is oxidized to albendazole sulfoxide (ASOX), a metabolite with an asymmetric sulfur center, which is present in plasma in the form of the (+) and (-) enantiomers (10–13) (Fig. 1). Marques et al (14) reported that in patients with neurocysticercosis, the plasma concentration of (+)-ASOX is approximately 10 times higher than that of the (-)-ASOX antipode. However, data on the absolute configuration and biologic activity of the individual enantiomers are lacking. The anthelminthic activity of albendazole resides both in its unaltered form and in the chiral ASOX metabolite. A recent study (13) on the participation of cytochrome P450 (CYP) and flavin-containing mono-oxygenases (FMO) in albendazole metabolism in human liver microsomes showed that the production of the ASOX metabolite is mediated by both systems but with a larger contribution of CYP (approximately 70%), mainly CYP3A4. Moroni et al (11), using rat liver microsomes, suggested that the enzymatic systems involved in the formation of (+)-ASOX and (-)-ASOX are different and provided evidence for the involvement of flavin-containing monooxygenases in the formation of the (+) enantiomer, of CYP2C6 and/or CYP2A in the formation of the (-) enantiomer, and of CYP3A in the formation of equivalent amounts of the (+)-ASOX and (-)-ASOX enantiomers.

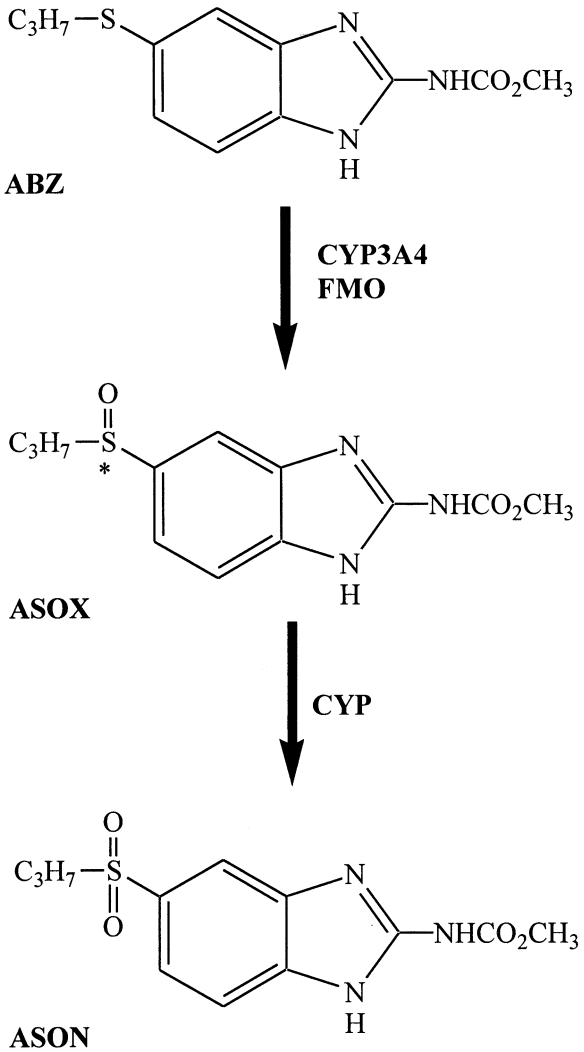

FIG. 1. Albendazole metabolism.

In patients with neurocysticercosis treated with albendazole for 8 days, approximately 8% of ASOX is oxidized to albendazole sulfone (ASON) (14) (see Fig. 1). The predominant sulfonation of one of the ASOX enantiomers may be the reason for the plasma enantiomer ratios differing from one ((+)-ASOX > (-)-ASOX). In rats, sulfonation depends on CYPc, the same isoform induced during repeated albendazole administration (12).

The characterization of the CYP isoforms involved in the enantioselective metabolism of albendazole to ASOX and of ASOX to ASON is especially important for the prediction of interactions with other drugs, particularly AEDs. Data obtained thus far on the interaction between drugs and albendazole metabolism do not discriminate between the enantiomers, with dexamethasone (15,16) (approximately 50%) and praziquantel (7) (4.5 times) showing an increase in plasma ASOX concentrations.

The clinical relevance of studies on the interaction between the AEDs carbamazepine, phenytoin, and phenobarbital and albendazole metabolism is based on the high frequency of the combined use of these drugs during the treatment of neurocysticercosis, because epileptic seizures constitute an important manifestation of the disease. Commonly used AEDs are eliminated through hepatic metabolism catalyzed by CYP3A4, CYP2C9, CYP2C19, and uridine diphosphate glucuronosyltransferase (UDPGT). Phenytoin, carbamazepine, and phenobarbital induce CYP and UDPGT. The knowledge of drug elimination pathways and their relative contribution to total drug clearance is essential in interpreting and anticipating clinical interactions (17–21).

Phenytoin has been frequently implicated in clinically significant drug interactions because of its narrow therapeutic index, slow absorption, and saturable metabolism. Phenytoin is eliminated by hydroxylation to p-hydroxyphenytoin by the CYP2C9 and CYP2C19 pathways, accounting for 70% to 90% of total clearance. Because of the difference in the K_M values, the CYP2C9 pathway may be saturated at steady-state therapeutic concentra-

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tions (10–20 μg/mL) of phenytoin, and the contribution of CYP2C19 to phenytoin metabolism should increase with increase in concentration within the therapeutic range. Phenytoin therapy significantly increases the amount and activity of CYP2C, CYP3A, UDPGT, and epoxide hydrolysis enzymes, enhancing the metabolism of many drugs. Phenytoin may compete with drugs metabolized by the same CYP isoenzymes (CYP2C9 and CYP2C19), decreasing their metabolic clearance (17–20,22).

Carbamazepine is metabolized by CYP3A4 and CYP2C8 to the stable carbamazepine-10,11-epoxide, a pharmacologically active compound accounting for about half of the total metabolism. Two other important carbamazepine metabolic pathways are oxidation to phenolic metabolites by CYP1A2 and direct N-glucuronidation. Carbamazepine induces drug metabolism by increasing both CYP (CYP2C, CYP3A) and UDPGT activities. Carbamazepine significantly enhances its own metabolism, more than doubling its clearance during the initial weeks of treatment (17–21).

Phenobarbital is eliminated both by hepatic metabolism and renal excretion. The main metabolic route is aromatic hydroxylation to p-hydroxy-phenobarbital by CYP2C19. This metabolite is in part conjugated to glucuronyl-p-hydroxy-phenobarbital. Another metabolic pathway is N-glucosylation to phenobarbital-glucoside. Phenobarbital increases the clearance of drugs eliminated metabolically by induction of CYP2C, CYP3A, epoxide hydrolysis, and UDPGT reactions. Like phenytoin, phenobarbital may compete with drugs metabolized by the same CYP isoenzymes, thus decreasing their metabolic clearance (17–20).

The aim of the current study was to assess the interaction between the AEDs phenytoin, carbamazepine, and phenobarbital and the enantioselective metabolism of albendazole in patients with neurocysticercosis. The clinical relevance of the investigation is based on the high frequency of the combined use of AEDs and albendazole during the treatment of neurocysticercosis and on the participation of CYP3A induced by AEDs in albendazole sulfoxidation.

MATERIALS AND METHODS

Patients and Clinical Protocol

The study was conducted on 32 adults with a diagnosis of the active form of intraparenchymatous neurocysticercosis assessed by computed tomography and/or nuclear magnetic resonance, and by enzyme-linked immunosorbent assays for cysticercosis in the cerebrospinal fluid. The patients were admitted to Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto-USP, for the 8 days of treatment with albendazole. All patients received detailed information about the objectives and procedures of the study and signed the Free and Informed Consent form.

The patients received albendazole (Zentel™ tablets; SmithKline Beecham Laboratórios; Rio de Janeiro, Brazil) at a dosage of 7.5 mg/kg every 12 hours for 8 days. The patients were divided into four groups based on the combined use of AEDs (Table 1). The control group consisted of nine patients who did not receive any AED. The phenytoin group consisted of nine patients treated with 200 to 300 mg/d sodium phenytoin (Hidantal™ tablets; Sarsa; Rio de Janeiro, Brazil) for a minimum of 3 months. The carbamazepine group consisted of nine patients treated with 600 to 1,200 mg/d carbamazepine (Tegretol™ tablets; Biogalênica; São Paulo, Brazil) for a minimum of 3 months. The phenobarbital group consisted of five patients treated with 100 to 300 mg/d phenobarbital (Gardenal™ tablets; Rhodia; São Paulo; Brazil) for a minimum of 3 months. The steady-state plasma concentrations of the AEDs on day 8 of albendazole

TABLE 1. *Patient characteristics*

	Control (n = 9)	Phenytoin (n = 9)	Carbamazepine (n = 9)	Phenobarbital (n = 5)
Sex	5 M, 4 F	4 M, 5 F	3 M, 6 F	3 M, 2 F
Age (years)	37.9 ± 8.8	35.4 ± 10.8	30.1 ± 6.6	38 ± 9.0
Weight (kg)	77.0 ± 28.7	65.3 ± 11.2	59.3 ± 10.8	71.4 ± 14.0
Antiepileptic drug concentration in plasma (μg/mL)	—	10.7 ± 1.7	6.9 ± 0.9 (1.2 ± 0.2)*	21.6 ± 4.2
Combined drugs	Dexamethasone, ranitidine, captopril	Dexamethasone, ranitidine, clobazam, clonazepam, propranolol	Dexamethasone, ranitidine, clobazam, methyldopa	Dexamethasone, ranitidine, clobazam, propranolol, nitrazepam

* Plasma carbamazepine-10,11-epoxide concentration.

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treatment are shown in Table 1. Thirteen of the 32 patients (4 patients in the control group, 5 in the phenytoin group, 3 in the carbamazepine group, and 1 in the phenobarbital group) were also treated with dexamethasone to prevent the acute inflammatory reaction caused by dead cysticerci.

Serial blood collections were carried out on day 8 of albendazole treatment during the last 12-hour dose interval. The patients fasted for 12 hours before and 3 hours after drug administration. Blood was collected with heparinized syringes (Liquemine™, 5,000 IU, Roche) at time 0, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after administration of the last albendazole dose. Plasma was centrifuged at 1,800*g* for 20 minutes and stored at −20°C until analysis.

Determination of the Anticonvulsant Drugs in Plasma

Carbamazepine, carbamazepine-10,11-epoxide (CBZ-E), phenytoin, and phenobarbital were measured using high-performance liquid chromatography (HPLC). Plasma samples of 500 μL were added to 2.5 μg of an internal standard solution (5-ethyl-5-toluyl barbituric acid) and 25 μL of 1 N HCl and extracted with 5.0 mL dichloromethane for 1 minute in a mixer. After centrifugation at 1,800*g* for 5 minutes and separation of the organic phases, the extracts were evaporated dry under an airflow. The pellets were reconstituted in 100 μL of the mobile phase and washed in 100 μL n-hexane. After shaking in a mixer for 20 seconds and centrifugation at 1,800*g* for 2 minutes, 20 μL of the upper phase was injected into the HPLC system. The anticonvulsant drugs were separated on a 125 × 4 mm C18 LichroCART™ (Merck; Darmstadt, Germany) reverse-phase column coupled to a similar precolumn (4 × 4 mm), using 0.25 N acetate buffer, pH 5.0 (73%), organic phase (20%; 91.5/8.5 acetonitrile/methanol, vol/vol) and isopropanol (7%) as the mobile phase, at a flow rate of 1.0 mL/min. The column effluent was monitored at 220 nm. The calibration curves were constructed by analyzing 500 μL blank plasma enriched with 25 μL of the appropriate carbamazepine (1.6–16 μg/mL plasma), CBZ-E (0.8–8 μg/mL plasma), phenytoin (3–30 μg/mL plasma), and phenobarbital (3–30 μg/mL plasma) working solutions. Absolute recovery was greater than 94% for all anticonvulsants. The method was linear for the concentration ranges of 0.6 to 36 μg/mL (carbamazepine), 0.3 to 16 μg/mL (CBZ-E), 1 to 60 μg/mL (phenytoin), and 1 to 60 μg/mL (phenobarbital). The coefficients of variation for intra-assay (n = 10) and interassay (n = 5) precision were less than 15%. The albendazole metabolites or other drugs commonly used in combination with albendazole for the treatment of neurocysticercosis did not interfere with the analytic method.

Determination of Metabolites in Plasma

Plasma albendazole metabolites were determined as previously described by us (23). Briefly, plasma aliquots of 500 μL were added to 200 μL of a sodium metabisulfite solution (4 mg/mL) and extracted with 3 mL ethyl acetate for 20 minutes (horizontal shaker, 220 ± 10 cycles/min). After centrifugation (10 minutes at 1,800*g*) and freezing of the aqueous phase (−20°C for 16 h), the organic phases (2 mL) were transferred to conic tubes and evaporated under an airflow at room temperature. The residues were reconstituted in 50 μL of the mobile phase, and 20-μL volumes were injected into the HPLC system. The albendazole metabolites were separated on a 4.6 × 250 mm Chiralpak™ AD chiral phase column (10-μm particles; Dialcel Chemical Industries Ltd., Los Angeles, CA, USA), equipped with a 4 × 4 mm CN Lichrospher™ 100 precolumn (5-μm particles; Merck), using n-hexane-isopropanol-ethanol (81:14.25:4.75, vol/vol/vol) as the mobile phase and a flow rate of 1.2 mL/min. The albendazole metabolites were detected by fluorescence at an excitation wavelength of 280 nm and an emission wavelength of 320 nm. The calibration curves were constructed for a concentration range of 5 to 500 ng of each ASOX enantiomer per milliliter of plasma and of 1 to 100 ng ASON per milliliter of plasma. Absolute recovery was greater than 92% for all albendazole metabolites. The quantification limit was 5 ng/mL for (+)-ASOX and (-)-ASOX and 1 ng/mL plasma for ASON. The method was linear up to 2,500 ng/mL plasma for each ASOX enantiomer and up to 500 ng/mL plasma for ASON. The coefficients of variation for intra-assay and interassay precision were less than 10%. Phenytoin, carbamazepine, phenobarbital, dexamethasone, and ranitidine, drugs generally used in combination with albendazole, did not interfere with the analytic method.

Pharmacokinetic and Statistical Analyses

The kinetic disposition of the albendazole metabolites was determined in the steady state during the 12-hour dose interval, using log curves of the plasma concentration (c) versus time (t) and the one-compartment model. The maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were obtained from the raw data of the individual patients. The c versus t area under the curve during the 12-hour dose interval (AUC^{0-12}) was determined by the trapezoid method. Apparent clearance

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(Cl/fm, where fm represents the fraction of the administered albendazole dose that reached the systemic circulation as a metabolite) was calculated by dividing the albendazole dose (mg/kg/12 h) by the AUC^{0-12} of the metabolite corrected for the molecular weight of albendazole. The sulfone formation capacity was defined as the $AUC_{ASON}/AUC_{ASOX} + AUC_{ASON}$ ratio. The formation half-life ($t_{1/2f}$) of each metabolite was obtained after correction of the formation curve by the residue method. The elimination half-life ($t_{1/2}$) was calculated using the end phase of the log c versus t curve. The rate constants (kf and k_{el}) were calculated using the $k = 0.693/t_{1/2}$ equation (14). The results are expressed as the mean (95% confidence interval). The data were analyzed by analysis of variance, followed by the Tukey-Kramer multiple comparisons test, with the level of significance set at 5%.

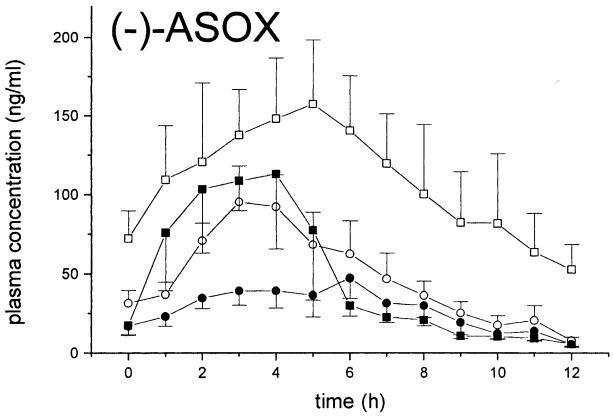

FIG. 3. Plasma concentration-time curves of (-)-albendazole sulfoxide (ASOX) during the 12-hour dose interval for untreated patients (□ control group) and patients treated with phenytoin (●), carbamazepine (◯), or phenobarbital (■). Data are reported as means ± standard error (n = 9).

RESULTS AND DISCUSSION

This study investigated the interaction between phenytoin, carbamazepine, and phenobarbital and the enantioselective metabolism of albendazole in patients with neurocysticercosis receiving AEDs for at least 3 months. The kinetic disposition of the albendazole metabolites was determined in the steady state during the 12-hour dose interval on day 8 of treatment of active neurocysticercosis.

Figures 2 to 4 show the high interindividual variability in the plasma concentrations of the albendazole metabolites, a consequence of the low solubility of albendazole in the gastrointestinal tract fluid and of the high presystemic elimination (8,14). In addition, the participation of CYP3A4 in the sulfoxidation of albendazole is suggested to be an important mechanism contributing to the variability in the pharmacokinetics of the albendazole metabolites. CYP3A4 is the most abundantly expressed CYP, accounting for approximately 30% to 40% of the total CYP content in human adult liver and small intestine. The intersubject variability in hepatic and intestinal CYP3A is considerable (5- to 10-fold). These differences are not well understood but clearly contribute to the variability in drug pharmacokinetics among patients (21).

Approximately 40% of the patients in this study (13/32) received dexamethasone during albendazole treatment due to an acute inflammatory reaction caused by dead cysticerci. Dexamethasone is metabolized extensively in human liver microsomes by CYP3A4 to

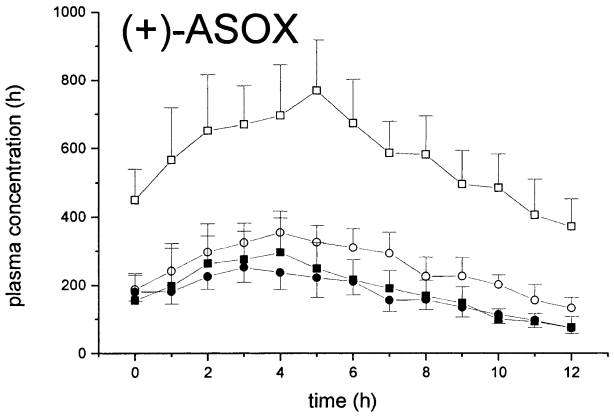

FIG. 2. Plasma concentration-time curves of (+)-albendazole sulfoxide (ASOX) during the 12-hour dose interval for untreated patients (□ control group) and patients treated with phenytoin (●), carbamazepine (◯), or phenobarbital (■). Data are reported as means ± standard error (n = 9).

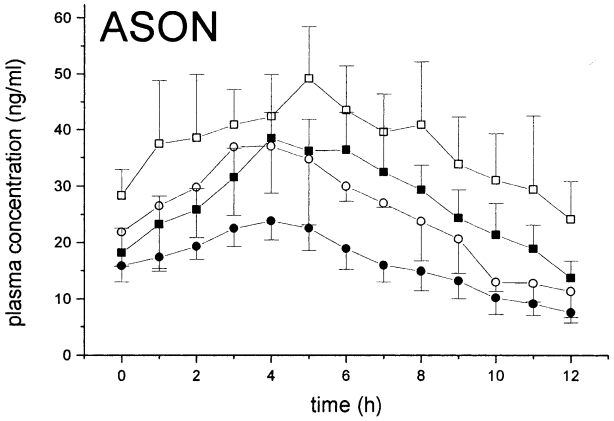

FIG. 4. Plasma concentration-time curves of albendazole sulfone (ASON) during the 12-hour dose interval for untreated patients (□ control group) and patients treated with phenytoin (●), carbamazepine (◯), or phenobarbital (■). Data are reported as means ± standard error (n = 9).

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TABLE 2. *Kinetic disposition of (+)-ASOX*

	Control (n = 9)	Phenytoin (n = 9)	Carbamazepine (n = 9)	Phenobarbital (n = 5)
C_{max} (ng/mL)	807.2 (538.5–1075.9)	279.4* (171.9–386.8)	408.4* (275.9–540.8)	286.5* (39.5–612.5)
t_{max} (h)	4.9 (3.4–6.4)	3.7 (2.3–5.2)	4.6 (3.4–5.8)	3.6 1.7–5.6)
$t_{1/2f}$ (h)	1.3 (0.9–1.6)	1.4 (1.0–1.7)	1.6 (1.1–2.1)	2.7 (0.9–6.2)
Kf (h^{-1})	0.6 (0.4–0.7)	0.6 (0.4–0.7)	0.5 (0.3–0.7)	0.7 (0.4–1.8)
$t_{1/2}$ (h)	8.0 (5.8–10.2)	3.8* (2.5–5.2)	4.1* (3.0–5.2)	4.9 (1.3–8.5)
kel (h^{-1})	0.09 (0.07–0.12)	0.20* (0.16–0.24)	0.19* (0.14–0.24)	0.18 (0.06–0.31)
AUC^{0-12} (ng.h/mL)	6,123.1 (3,270.3–8,975.9)	2,115.4* (1,316.7–2,914.1)	3,098.2* (1,924.7–4,271.7)	2,432.4* (146.1–4,718.7)
Cl/fm ($l.h^{-1}.kg^{-1}$)	2.4 (0.9–3.8)	5.1 (2.1–8.1)	3.4 (1.7–5.1)	4.8 (1.2–8.5)

* $P < 0.05$, Tukey-Kramer multiple comparisons test.
Data are reported as means (95% confidence interval).

6-hydroxy products (24). McCune et al (25) showed that clinically relevant doses of dexamethasone increase hepatic CYP3A4 activity by an average of 25.7%, with significant variability in the degree of CYP3A4 induction ranging from no increase to a 70% increase in CYP3A4 activity. Dexamethasone increases plasma ASOX concentrations in patients treated with albendazole (15,16). Moroni et al (11) reported that dexamethasone induces CYP3A1 in rat liver microsomes and is responsible for a fourfold increase in albendazole sulfoxidation. Based on the observations by Marques et al (14), dexamethasone does not alter the (+)/(-) enantiomeric ratio of the ASOX metabolite in patients with neurocysticercosis, a result that agrees with the finding that in rat liver microsomes, CYP3A1 is involved in the formation of equivalent amounts of the (+)-ASOX and (-)-ASOX enantiomers. However, patients treated or not with dexamethasone were included in the control and phenytoin, carbamazepine, and phenobarbital groups.

The pharmacokinetic parameters that characterize the formation rate of the (+)-ASOX and (-)-ASOX metabolites (i.e., formation half-life, formation rate constant, and time to reach the maximum plasma concentration) were not altered by the administration of phenytoin, carbamazepine, or phenobarbital (Tables 2 and 3). These parameters are influenced not only by the rate of ASOX formation but also by the variable absorption rate of albendazole. Based on the fact that phenytoin, carbamazepine, and phenobarbital are inducers of CYP3A4 (17, 18,21), and considering the predominant participation of this isoform in the formation of the ASOX metabolite in human liver microsomes (13), relevant alterations in the formation rate of both ASOX metabolites were expected.

The plasma AUC^{0-12}, calculated for the 12-hour dose interval, was significantly reduced ($P < 0.05$) in the phenytoin, carbamazepine, and phenobarbital groups (control 6.1, phenytoin 2.1, carbamazepine 3.1, and phenobarbital 2.4 μg/h/mL; see Table 2). C_{max} was also reduced in all groups of patients receiving AEDs. No significant difference in the AUC^{0-12} or C_{max} parameters was observed between the groups treated with the different AEDs, suggesting that phenytoin, carbamazepine, and phenobarbital induce the oxidative metabolism of albendazole to the same extent. An approximately 50% reduction in the elimination half-life of (+)-ASOX was observed for the phenytoin and carbamazepine groups (control 8.0, phenytoin 3.8, and carbamazepine 4.1 h; see Table 2). The elimination half-life of approximately 5 hours obtained by Marques et al (14) in a study of patients with neurocysticercosis treated with albendazole as

TABLE 3. *Kinetic disposition of (−)-ASOX*

	Control (n = 9)	Phenytoin (n = 9)	Carbamazepine (n = 9)	Phenobartial (n = 5)
C_{max} (ng/mL)	243.7 (147.2–340.1)	55.9* (29.6–82.2)	109.7* (57.6–161.9)	122.6* (13.2–231.9)
t_{max} (h)	4.6 (2.5–6.7)	3.7 (1.8–5.6)	3.7 (2.5–4.9)	2.6 (1.6–3.5)
$t_{1/2f}$ (h)	1.3 (1.0–1.5)	1.1 (0.7–1.5)	1.3 (0.9–1.7)	1.3 (0.8–1.7)
K_f (h^{-1})	0.5 (0.4–0.7)	0.7 (0.5–1.0)	0.7 (0.4–0.9)	0.6 (0.3–0.9)
$t_{1/2}$ (h)	4.3 (2.6–6.0)	1.9* (1.3–2.5)	2.2* (1.2–3.2)	2.1* (1.5–2.6)
kel (h^{-1})	0.2 (0.1–0.3)	0.4* (0.3–0.6)	0.3 (0.3–0.4)	0.3 (0.3–0.4)
AUC^{0-12} (ng.h/mL)	1,792.9 (1,188.4–2,397.5)	415.7* (141.7–689.8)	573.9* (296.3–851.4)	496.7* (127.9–865.5)
Cl/fm ($l.h^{-1}.kg^{-1}$)	5.3 (3.3–7.3)	29.9* (12.8–47.1)	18.8 (11.2–26.5)	22.2 (4.1–40.3)
(+)/(−) AUC^{0-12}	5.2 (2.3–8.2)	9.0 (3.4–14.6)	6.0 (4.6–7.4)	5.1 (1.9–8.2)

* $P < 0.05$, Tukey-Kramer multiple comparisons test.
Data are reported as means (95% confidence interval).

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a multiple-dose regimen was probably due to the inclusion of patients treated with AEDs and not only to the self-induction of albendazole metabolism, as previously suggested. The elimination half-life of 8 hours (95% confidence interval, 6–10 h) observed here for the control group agrees with the 6 to 15 hours reported by Sotelo and Jung (5).

The observations concerning (+)-ASOX are also valid for the (-)-ASOX antipode. Phenytoin, carbamazepine, and phenobarbital significantly reduced AUC^{0-12} (control 1.8, phenytoin 0.4, carbamazepine 0.6, phenobarbital 0.5 μg/h/mL), C_{max} (control 0.24, phenytoin 0.06, carbamazepine 0.11, phenobarbital 0.12 μg/mL), and elimination half-life (control 4.3, phenytoin 1.9, carbamazepine 2.2, phenobarbital 2.1 h) (see Table 3).

Marques et al (14) showed enantioselectivity in the kinetic disposition of ASOX in patients with neurocysticercosis, with plasma concentrations of (+)-ASOX 10 times higher than those observed for the (-)-ASOX antipode. Delatour et al (10) obtained enantiomeric ratios of up to 13.1 in healthy volunteers treated with a single dose of albendazole. The (+)/(-) enantiomeric ratios referring to the AUC^{0-12} parameter were not altered by the administration of phenytoin, carbamazepine, or phenobarbital (see Table 3). These data agree with the observation that these AEDs induce ASOX metabolism in a nonenantioselective manner.

Moroni et al (11), using liver microsomes of rats previously treated with phenobarbital, observed a twofold increase in the production of (-)-ASOX, together with a reduction in the formation of the (+)-ASOX antipode. They suggested that the limited effect of phenobarbital on the metabolism of albendazole in rats is due to the induction, to a small extent, of CYP2A1, CYP2C6, and CYP3A, enzymes involved in albendazole metabolism. Treatment of rats with phenobarbital results in the induction, to a larger extent, of CYP2B1 and CYP2B2. The data obtained in the current study for patients with neurocysticercosis treated with phenobarbital showed a reduction in the plasma concentrations (AUC^{0-12} and C_{max}) of both (+)-ASOX and (-)-ASOX, with evidence of induction during metabolism (see Tables 2 and 3).

The approximately 6% sulfonation capacity observed for the control group was not altered in the groups of patients treated with phenytoin, carbamazepine, or phenobarbital. However, Table 4 shows a significant reduction ($P < 0.05$) in plasma ASON concentration-versus-time area under the curve (AUC^{0-12}) for the patients treated with phenytoin (control 0.5 vs. phenytoin 0.2 μg/mL) and in elimination half-life for the groups treated with phenytoin and carbamazepine (control 8.0, phenytoin 3.8, carbamazepine 4.1 h), suggesting that phenytoin and carbamazepine are also inducers of the ASON metabolism. With respect to phenobarbital, no significant alterations in plasma concentrations (AUC^{0-12}) or elimination half-life of the ASON metabolite were observed.

The present results suggest that phenytoin, carbamazepine, and phenobarbital induce, to approximately the same extent, the oxidative metabolism of albendazole in a nonenantioselective manner. The mechanism of interaction is based on the fact that phenytoin, carbamazepine, and phenobarbital are inducers of CYP3A, an enzyme involved in the sulfoxidation of albendazole in humans. The observed alterations in plasma ASON concentrations, especially in the group treated with phenytoin, indicate that the AEDs also induce CYP2C. However, no data on the CYP isoforms involved in ASOX oxidation are available.

Finally, patients treated with AEDs that induce CYP3A and CYP2C show a significant reduction in plasma (+)-ASOX and (-)-ASOX concentrations. This fact may compromise the efficacy of albendazole in the treatment of neurocysticercosis, and higher doses would be necessary when albendazole is coadministered with AEDs.

TABLE 4. *Kinetic disposition of ASON*

	Control (n = 9)	Phenytoin (n = 9)	Carbamazepine (n = 9)	Phenobarbital (n = 5)
C_{max} (ng/mL)	807.2 (538.5–1075.9)	279.4* (171.9–386.8)	408.4* (275.9–540.8)	286.5* (39.5–612.5)
t_{max} (h)	4.9 (3.4–6.4)	3.7 (2.3–5.2)	4.6 (3.4–5.8)	3.6 (1.7–5.6)
$t_{1/2f}$ (h)	1.3 (0.9–1.6)	1.4 (1.0–1.7)	1.6 (1.1–2.1)	2.7 (0.9–6.2)
Kf (h^{-1})	0.6 (0.4–0.7)	0.6 (0.4–0.7)	0.5 (0.3–0.7)	0.7 (0.4–1.8)
$t_{1/2}$ (h)	8.0 (5.8–10.3)	3.8* (2.5–5.2)	4.1* (3.0–5.2)	4.9 (1.3–8.5)
kel (h^{-1})	0.09 (0.07–0.12)	0.20* (0.16–0.24)	0.19* (0.14–0.24)	0.18 (0.06–0.31)
AUC^{0-12} (ng.h/ml)	491.4 (312.3–670.5)	197.4* (128.5–266.4)	324.5 (207.2–441.7)	304.1 (73.1–535.1)
Cl/fm ($l.h^{-1}.kg^{-1}$)	22.9 (12.1–33.6)	49.8* (31.4–68.2)	3.19 (20.4–43.4)	33.7 (18.0–49.5)
Sulfone formation (%)	5.7 (3.5–8.0)	7.0 (5.2–8.7)	8.1 (6.5–9.7)	10.2 (4.7–15.6)

* $P < 0.05$, Tukey-Kramer multiple comparisons test.
Data are reported as means (95% confidence interval).

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Acknowledgments: The authors are grateful to FAPESP (Fundação de Amparo a Pesquisa do Estado de São Paulo) for financial support and to CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) for granting research fellowships. The authors thank Mrs. Andréia M. Pontoglio for her technical assistance.

REFERENCES

1. Takayanagui OM, Jardim E. Therapy for neurocysticercosis. Comparison between albendazole and praziquantel. *Arch Neurol* 1992; 49:290–4.
2. Del Brutto OH, Sotelo J, Roman GC. Therapy for neurocysticercosis: a reappraisal. *Clin Infect Dis* 1993;17:730–5.
3. Garcia HH, Gilman RH, Horton J, et al. Albendazole therapy for neurocysticercosis: a prospective double-blind trial comparing 7 *versus* 14 days of treatment. *Neurology* 1997;48:1421–7.
4. Rousseau MC, Guillotel B, Delmont J. Neurocysticercosis in the southeast of France, 1988–1998. *Presse Med* 1999;28:2141–4.
5. Sotelo J, Jung H. Pharmacokinetics optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998;34:503–15.
6. Herrera LA, Benitez-Bribiesca L, Sotelo J, et al. Chemotherapy of cysticercosis. *Gac Med Mex* 2000;136:477–89.
7. Homeida M, Leahy W, Copeland S, et al. Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. *Ann Trop Med Parasitol* 1994;88:551–9.
8. Marriner SE, Morris DL, Dickson B, et al. Pharmacokinetics of albendazole in man. *Eur J Clin Pharmacol* 1986;30:705–8.
9. Steiger U, Cotting J, Rechen J. Albendazole treatment of echinococcosis in humans: effects on microsomal metabolism and drug tolerance. *Clin Pharmacol Ther* 1990;47:347–53.
10. Delatour P, Benoit E, Besse S, et al. Comparative enantioselectivity in the sulphoxidation of albendazole in man, dogs and rats. *Xenobiotica* 1991;21:217–21.
11. Moroni P, Buronfosse T, Longin-Sauvageon C, et al. Chiral sulfoxidation of albendazole by the flavin adenine dinucleotide-containing and cytochrome P450-dependent mono-oxygenases from rat liver microsomes. *Drug Metab Dispos* 1995;23:160–4.
12. Souhaili-El Amri H, Mothe O, Totis M, et al. Albendazole sulfonation by rat liver cytochrome P-450c. *J Pharmacol Exp Ther* 1988;246:758–64.
13. Rawden HC, Kokwaro GO, Ward SA, et al. Relative contribution of cytochromes P-450 and flavin-containing mono-oxygenases to the metabolism of albendazole by human liver microsomes. *Br J Clin Pharmacol* 2000;49:313–22.
14. Marques MP, Takayanagui OM, Bonato PS, et al. Enantioselective kinetic disposition of albendazole sulfoxide in patients with neurocysticercosis. *Chirality* 1999;11:218–23.
15. Jung H, Hurtado M, Medina MT, et al. Dexamethasone increases plasma levels of albendazole. *J Neurol* 1990;231:279–80.
16. Takayanagui OM, Lanchote VL, Marques MPC, Bonato PS. Therapy for neurocysticercosis: pharmacokinetic interaction of albendazole sulfoxide with dexamethasone. *Ther Drug Monit* 1997; 19:51–5.
17. Lin JH, Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. *Clin Pharmacokinet* 1998;35:361–90.
18. Riva R, Albani F, Contin M, et al. Pharmacokinetic interactions between antiepileptic drugs. *Clin Pharmacokinet* 1996;31:470–93.
19. Tanaka E. Clinically significant pharmacokinetic drug interactions between antiepileptic drugs. *Clin Pharmacol Ther* 1999;24:87–92.
20. Taylor WJ, Robson JD, Spivey-Miller S. *Handbook of Therapeutic Monitoring*, 2d ed. Cincinnati: Harvey Whitney Books Company, 1993.
21. Wildt SN, Kearns GL, Leeder JS, et al. Cytochrome P450 3A. Ontogeny and drug disposition. *Clin Pharmacokinet* 1999;37:485–505.
22. Donahue SR, Flockhart DA, Abernehty DR, et al. Ticlopidine inhibition of phenytoin metabolism mediated by potent inhibition of CYP2C19. *Clin Pharmacol Ther* 1997;62:572–7.
23. Lanchote VL, Marques MPC, Takayanagui OM, et al. Simultaneous determination of albendazole sulfoxide enantiomers and albendazole sulfone in plasma. *J Chromatogr B* 1998; 709:273–9.
24. Gentle DM, Tomlinson ES, Maggs JL, et al. Dexamethasone metabolism by human liver in vitro. Metabolite identification and inhibition of 6-hydroxylation. *J Pharmacol Exp Ther* 1996;277: 105–12.
25. Mccune JS, Hawke RL, Lecluyse EL, et al. In vivo and in vitro induction of human cytochrome P4503A4 by dexamethasone. *Clin Pharmacol Ther* 2000;68:356–66.

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