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Albendazole metabolism in patients with neurocysticercosis: antipyrine as a multifunctional marker drug of cytochrome P450

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Abstract

The present study investigates the isoform(s) of cytochrome P450 (CYP) involved in the metabolism of albendazole sulfoxide (ASOX) to albendazole sulfone (ASON) in patients with neurocysticercosis using antipyrine as a multifunctional marker drug. The study was conducted on 11 patients with neurocysticercosis treated with a multiple dose regimen of albendazole for 8 days (5 mg/kg every 8 h). On the 5th day of albendazole treatment, 500 mg antipyrine was administered *po*. Blood and urine samples were collected up to 72 h after antipyrine administration. Plasma concentrations of (+)-ASOX, (-)-ASOX and ASON were determined by HPLC using a chiral phase column and detection by fluorescence. The apparent clearance (CL/f) of ASON and of the (+) and (-)-ASOX enantiomers were calculated and compared to total antipyrine clearance (CL_T) and the clearance for the production of the three major antipyrine metabolites (CL_m). A correlation ($P \leq 0.05$) was obtained only between the CL_T of antipyrine and the CL/f of ASON ($r = 0.67$). The existence of a correlation suggests the involvement of CYP isoforms common to the metabolism of antipyrine and of ASOX to ASON. Since the CL_T of antipyrine is a general measure of CYP enzymes but with a slight to moderate weight toward CYP1A2, we suggest the involvement of this enzyme in ASOX to ASON metabolism in man. The study supports the establishment of a specific marker drug of CYP1A2 in the study of the *in vivo* metabolism of ASOX to ASON.

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- Albendazole
- Cysticercosis
- Enantiomers
- Antipyrine
- Cytochrome P450
- CYP
- Patients

Introduction

Albendazole is a drug considered to be effective for the treatment of parenchymal brain neurocysticercosis, an infestation of the central nervous system by the larval form of *Taenia solium* (1-3). Albendazole is rapidly transformed by flavin mono-oxygenases (FMO) and by the cytochrome P450 (CYP) system into the chiral metabolite albendazole sulfoxide [(+)-ASOX; (-)-ASOX)], which possesses antihelminthic activity, and into the non-chiral metabolite albendazole sulfone (ASON) which lacks pharmacologic activity (3-5) (Figure 1). The kinetic disposition of ASOX is enantioselective with (+)/(-)

ratios of area under the plasma concentration-time curve (AUC) of approximately 10 in patients with neurocysticercosis treated with albendazole (6,7).

Moroni et al. (8) reported that in rat liver microsomes FMO favors the formation of (+)-ASOX, while CYP2C6 and/or CYP2A1 favor the production of (-)-ASOX and CYP3A leads to the formation of equivalent quantities of the (+) and (-) enantiomers. Rawden et al. (5) observed that in human liver microsomes the production of ASOX depends on FMO3, CYP3A4 and CYP1A2, but mainly CYP3A4. Amri et al. (9) reported the involvement of CYP in albendazole sulfonation in rats and Benoit et al. (10) concluded that CYP is induced by albendazole and is responsible for the increase in ASON production specifically using (-)-ASOX as a substrate. Autoinduction during albendazole metabolism has been reported in *in vivo* and *in vitro* studies in animals and in man (4,9-11).

Antipyrine is a marker drug extensively used in studies on the capacity of hepatic oxidative metabolism. More than 90% of the antipyrine dose administered is excreted into the urine in the form of its metabolites, with the main products being norantipyrine (NORA), 4-hydroxyantipyrine (OHA) and 3-hydroxymethylantipyrine (HMA) (12). Engel et al. (13), using human liver microsomes, showed that at least six CYP isoforms are involved in the metabolism of antipyrine. 4-Hydroxylation is mainly dependent on CYP3A4 and, to a lesser extent, on CYP1A2. The formation of NORA mainly depends on CYP2C as well as on CYP1A2, whereas CYP1A2 and CYP2C9 are involved in the formation of HMA. In addition to the isoforms reported by Engel et al. (13), Sharer and Wrighton (14) also observed the involvement of CYP2A6 in OHA formation and of CYP2E1 in HMA formation. As a consequence of the multiplicity of the enzymes involved in the formation of each metabolite, there is no absolute specificity of the clearances for production of metabolites in studies on the activity of specific CYP isoforms. Total antipyrine clearance reflects the sum of the activities of enzymes involved in the formation of all three metabolites, but with a slight to moderate weight of catalysis carried by CYP1A2 (14).

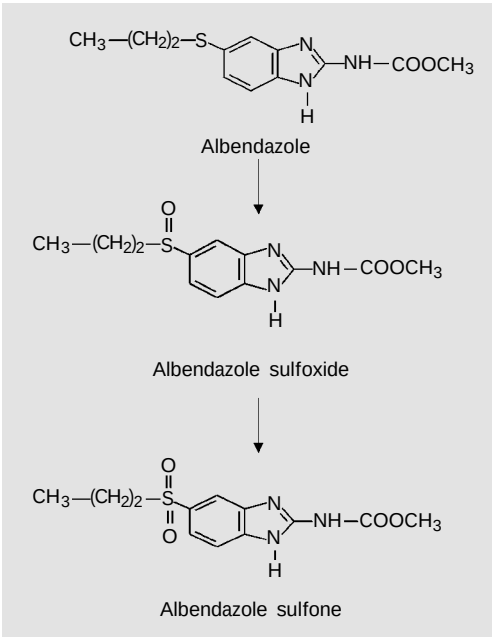

Figure 1. Albendazole metabolism (15).

The sulfoxidation of albendazole in human liver microsomes is mediated by both FMO and CYP, mainly by CYP3A4 (5). There are no data regarding the isoform(s) of CYP involved in the sulfonation of ASOX in man.

In view of the importance of this knowledge for the prediction of interactions of albendazole with commonly combined drugs such as dexamethasone, antiepileptics and H_2 receptor antagonists, the objective of the present study was to determine the isoform(s) of CYP involved in the metabolism of albendazole in patients with neurocysticercosis using antipyrine as a marker drug.

Material and Methods

Study design

The study was conducted on 11 patients

with a diagnosis of the active form of intraparenchymatous neurocysticercosis, which was confirmed by a clinical picture compatible with the disease, by computed tomography (CT) and/or magnetic resonance imaging (MRI), and by ELISA for cysticercosis in the cerebrospinal fluid. Adult patients of both sexes (5 men and 6 women) with cardiac, hepatic and renal function within normal limits were included in the study. A combination of dexamethasone, antiepileptics and H_2 receptor antagonists during treatment with albendazole was required by various patients (Table 1).

Albendazole (5 mg/kg, Zentel®, tablets; SmithKline Beecham Laboratórios Ltda., Rio de Janeiro, RJ, Brazil) was administered orally 3 times per day for 8 days. Heparinized blood samples were collected after administration of the last albendazole dose at time 0, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h. Plasma was obtained by centrifugation for 20 min at 1800 *g* and stored at -20ºC. A single dose of antipyrine (500 mg, gelatin capsule) was administered orally to the patients on the morning of the 5th day of albendazole treatment. Heparinized blood samples were obtained at time 0, and at 24, 48 and 72 h and plasma was obtained by centrifugation for 20 min at 1800 *g* and stored at -20ºC. Urine samples were collected 0-24, 24-48 and 48-72 h after antipyrine administration into 1-liter amber flasks containing 4 g sodium metabisulfide to avoid oxidation of the antipyrine metabolites. Each urine sample was homogenized, its volume determined and an aliquot was stored at -20ºC.

The patients were admitted to Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, USP, for the 8 days of treatment. All patients received detailed information about the study and gave written informed consent to participate in the study. The study protocol was approved by the Ethics Committee of the local hospital.

Chromatographic analysis

Chemicals and drugs. The racemic ASOX (99.4%) and ASON (99.8%) standards were purchased from Robert Young & Co. Ltd. (Glasgow, Scotland). Antipyrine (100%) was purchased from Sigma (St. Louis, MO, USA), NORA (99%) and OHA (99%) from Aldrich Chemical Company (Milwaukee, WI, USA), and HMA was kindly provided by Professor D.D. Breimer (Center for Bio-Pharmaceutical Sciences, Leiden University, The Netherlands). All reagents and solvents (chroma-

Table 1. Characteristics of the patients (N = 11).

Patient	Sex	Age (years)	Weight (kg)	Combined drugs
1	M	46	80.0	nifedipine, phenytoin, ranitidine, dextrochlorpheniramine
2	M	42	90.0	phenytoin, dexamethasone, ranitidine
3	M	24	64.9	dexamethasone, phenytoin
4	F	31	51.0	phenytoin
5	M	-	49.7	carbamazepine, phenytoin, ranitidine
6	M	67	59.7	metoprolol, carbamazepine, dextrochlorpheniramine
7	F	39	62.2	acetylsalicylic acid
8	F	46	83.0	dexamethasone, ranitidine
9	F	41	66.7	dexamethasone, ranitidine, amitriptyline
10	F	22	67.0	dexamethasone, phenytoin
11	F	40	72.0	carbamazepine, ranitidine, dexamethasone
Mean ± SD		39.8 ± 12.8	67.8 ± 12.7	

F, female; M, male.

tographic grade) used for sample preparation and as mobile phase in the chromatographic systems were purchased from Merck (Darmstadt, Germany).

Measurement of (+)-ASOX, (-)-ASOX and ASON in plasma. Plasma (+)-ASOX, (-)-ASOX and ASON were analyzed by the method of Lanchote et al. (15). A 500-µl plasma sample supplemented with sodium metabisulfite was extracted with ethyl acetate and analyzed by HPLC using a Shimadzu apparatus (Kyoto, Japan) equipped with an LC-10AS solvent pump, a Rheodyne model 7125 (Cotati, CA, USA) injector with a 20-µl loop, an RF 551 fluorescence detector (λ_{exc} = 280 nm and λ_{emis} = 320 nm), and a CR6 integrator. The analysis was performed using a 250 x 4.6 mm Chiralpak® AD column (Chiral Technologies, Exton, PA, USA) protected with a 4 x 4 mm CN precolumn (Merck), with the mobile phase consisting of a mixture of n-hexane:isopropanol:ethanol (81:14.25:4.75, v/v/v) at a flow rate of 1.2 ml/min. Albendazole metabolites were eluted from the chiral column in the following sequence: (+)-ASOX (13.7 min), (-)-ASOX (21.6 min) and ASON (25.7 min). Linear standard curves were obtained in the concentration range of 5-2500 ng/ml for ASOX enantiomers and in the concentration range of 1-500 ng/ml for ASON. The lower concentrations in the calibration curves were considered to be the quantification limit of the method, i.e., 5 ng/ml for both ASOX enantiomers and 1 ng/ml for ASON.

Measurement of antipyrine and its major metabolites in urine. Urine antipyrine and its metabolites HMA, NORA and OHA were analyzed as described by Lanchote et al. (16). A 500-µl urine sample supplemented with 0.25 M acetate buffer, pH 5.0, containing sodium metabisulfite was submitted to enzymatic hydrolysis (Limpet acetone powder type 1: *Platela vulgata*; Sigma) for 2 h at 37ºC and extracted at pH 5 with dichloromethane:isopropanol (9:1, v/v). The samples were then analyzed by HPLC (Shimadzu) using an LC-10AD solvent pump, a Rheodyne model 7125 manual injector with a 20-µl loop, a model SPD-10A ultraviolet detector set at 254 nm, and a CR6 integrator. Antipyrine and related compounds were separated on a Nova Pak® C18 60 A 4-µm column (3.9 x 150 mm; Waters Corporation, Milford, MA, USA), with the mobile phase consisting of 0.25 N acetate buffer, pH 5.0, and methanol (77:23, v/v), at a flow rate of 1.0 ml/min. Only 5-min runs were necessary for the elution of HMA (1.7 min), antipyrine (3.3 min), NORA (3.7 min) and OHA (4.3 min). Calibration curves were constructed for concentrations of 2.0 to 10.0 µg antipyrine/ml urine and 8.0 to 20.0 µg of each antipyrine metabolite/ml urine. The method permits the quantification of concentrations as low as 1.25 µg/ml for antipyrine, 2.5 µg/ml for NORA and 5.0 µg/ml for OHA and HMA.

Measurement of antipyrine in plasma. Plasma antipyrine was determined as described by Lanchote et al. (17). A 500-µl plasma sample supplemented with 12.5 µg phenacetin (internal standard) was extracted with chloroform:ethanol (9:1, v/v) in acid medium, pH 5.0, and analyzed by HPLC using a Rheodyne manual injector with a 20-µl loop and an ultraviolet detector (Shimadzu, model SPD-10A) set at 254 nm. Samples were analyzed on a Nova-Pak® C18 60 A 4-µm column (3.9 x 150 mm, Waters), with the mobile phase consisting of 0.25 N acetate buffer, pH 5.0, and methanol (65:35, v/v), at a flow rate of 1.0 ml/min. The mean retention times of antipyrine and internal standard were 2 and 3 min, respectively. A calibration curve was constructed for concentrations of 0.04 to 0.8 µg antipyrine/ml plasma. The limit of quantification for this assay was set at 0.025 µg/ml.

Pharmacokinetic analysis

The areas under the plasma albendazole metabolite concentration-time curves were

calculated by the trapezoidal rule at a dose interval of 8 h (AUC_{SS}^{0-8}). Apparent clearances (CL/fm) of (+)-ASOX, (-)-ASOX and ASON were calculated as the ratio of albendazole dose corrected as a function of molecular weight of the metabolite to AUC_{SS}^{0-8}. The fm parameter represents the albendazole fraction that reaches the systemic circulation as a metabolite (18).

The area under the plasma antipyrine concentration-time curve ($AUC^{0-\infty}$) was calculated by the trapezoidal rule including extrapolation to infinite using the last plasma concentration divided by the elimination rate constant (Kel). Elimination half-life (t1/2) was calculated directly from the plasma concentration-time curve and the elimination rate constant was calculated using the equation 0.693/t1/2. Total clearance (CL_T) was calculated by dividing the dose by the $AUC^{0-\infty}$ and apparent volume of distribution (Vd) as the ratio of the total clearance and elimination rate constant. Bioavailability was considered to be 100%. Rates of formation of antipyrine metabolites were expressed as clearances for production of metabolites (CL_m) calculated by dividing the amount of antipyrine excreted in urine as a metabolite by the AUC of antipyrine (18,19).

Statistical analysis

Median and mean values, 95% confidence interval (95% CI) and standard error of the mean (SEM) were determined with the GraphPad Instat® software. The plasma concentration (+)-ASOX/(-)-ASOX ratios were analyzed using the paired *t*-test, with the level of significance set at $P \leq 0.05$. Correlation and orthogonal regression analyses were performed according to the equations described by Schellens et al. (20).

Results and Discussion

Approximately 70% of human liver CYP is accounted for by CYP1A2, CYP2A6, CYP2B6, CYP2C, CYP2D6, CYP2E and CYP3A enzymes (21). CYP3A is the most abundantly expressed subfamily in the liver, comprising 25 to 40% of the total CYP. The intersubject variability in hepatic and intestinal CYP3A activity is considerable (5- to 10-fold) and clearly contributes to variability in drug response among patients (22).

Antipyrine is undoubtedly the most commonly used substrate for estimating the influence of endogenous and exogenous factors on CYP activities. Antipyrine can be considered a multifunctional substrate since assessment of clearances for formation of its different metabolites provides information on different CYP isoforms while total antipyrine clearance is a general measure of CYP with a slight to moderate weight toward CYP1A2 (14).

The investigation of the relationship between apparent clearance of albendazole metabolites versus total antipyrine clearance and/or clearance for production of antipyrine metabolites requires the application of orthogonal regression analysis since both variables are prone to errors. Considering that total clearance or clearance for production of metabolites reflects the activity of the enzyme, correlation and orthogonal regression analyses may indicate that the substrates or metabolites studied are oxidized and respectively formed by the same or similar CYP isoforms (20).

The pharmacokinetic parameters regarding the kinetic disposition of unchanged and biotransformed antipyrine and the data on apparent clearance of albendazole metabolites are reported in Tables 2 and 3, respectively, as mean (95% CI) and median for the 11 patients with neurocysticercosis. The plasma concentration-time curves for albendazole metabolites are reported in Figure 2 as mean ± SEM. The orthogonal regression equations and correlation coefficients calculated between apparent clearance (albendazole metabolites) and total clearance (antipyrine) or clearance for production of meta-

Table 2. Kinetic disposition of unchanged and biotransformed antipyrine.

Parameters	Antipyrine	HMA	NORA	OHA
t1/2 (h)	9.95 (7.88-12.03) 9.00	23.09 (14.28-31.90) 20.00	18.63 (8.16-29.11) 12.00	12.45 (8.78-16.13) 10.00
Kel x 10^{-1} (h^{-1})	0.75 (0.61-0.90) 0.77	0.39 (0.26-0.53) 0.35	0.51 (0.36-0.67) 0.58	0.64 (0.49-0.79) 0.69
Vd (l/kg)	1.24 (0.70-1.77) 0.82	-	-	-
$AUC^{0-\infty}$ (µg h^{-1} ml^{-1})	53.63 (26.26-81.01) 38.83	-	-	-
CL_T (l h^{-1} kg^{-1})	0.23 (0.10-0.35) 0.18	-	-	-
CL_m (l h^{-1} kg^{-1})	-	0.05 (0.01-0.09) 0.03	0.03 (0.01-0.05) 0.01	0.05 (0.03-0.07) 0.04
Fel (%)	2.71 (1.17-4.26) 1.90	21.02 (11.55-30.48) 18.00	13.83 (7.22-20.45) 9.90	21.12 (11.74-30.51) 19.40

Data are reported as mean (95% CI) and median (N = 11). HMA, 3-hydroxymethylantipyrine; NORA, norantipyrine; OHA, 4-hydroxyantipyrine; t1/2 = elimination half-life; Kel = elimination rate constant; Vd = volume of distribution; $AUC^{0-\infty}$ = area under the plasma concentration-time curve; CL_T = total clearance; CL_m = clearance for metabolite production; Fel = dose fraction excreted into urine.

Table 3. Apparent clearance of albendazole metabolites.

	CL/fm (ml min^{-1} kg^{-1})
(+)-ASOX	47.72 (24.46-70.97) 44.24
(-)-ASOX	497.89 (221.78-774.00) 499.02
ASON	1016.80 (445.67-1587.90) 696.04

Data are reported as mean (95% CI) and median (N = 11). CL/fm = albendazole dose corrected as a function of metabolite molecular weight/metabolite AUC at a dose interval of 0-8 h. ASOX = albendazole sulfoxide; ASON = albendazole sulfone.

bolite (antipyrine metabolites) parameters are shown in Table 4. The correlation coefficients indicated a correlation ($P \leq 0.05$) only between total antipyrine clearance and apparent clearance of ASON, while no correlation was found between the other clearances. This correlation suggests the involvement of common CYP isoforms in the metabolism of antipyrine and of ASOX to ASON. In rats, CYP1A is involved in the elimination of ASOX to ASON (4,9,10).

There are no data in the literature about the influence of neurocysticercosis on the kinetic disposition of ASOX and ASON. Marriner et al. (23) investigated the pharmacokinetics of albendazole in healthy volunteers (N = 10) after an oral dose of 400 mg albendazole and reported extremely variable AUC values (0.42-8.95 µg h^{-1} ml^{-1}). The authors did not describe CL/f or Vd/f parameters. Sánchez et al. (24) investigated patients with a diagnosis of parenchymal brain cysticercosis treated with albendazole at 15 mg kg^{-1} day^{-1} for 13 days and reported CL/f values ranging from 0.54 to 5.56 l kg^{-1} h^{-1}. Steady-state concentrations of ASOX vary widely among individuals (3,7), probably due to the low solubility of albendazole in the gastrointestinal tract (3). Takayanagui et al. (25) reported the pharmacokinetic interaction of ASOX with dexamethasone combined or not with cimetidine in patients with active intraparenchymal brain cysticercosis and reported similar clearance values (0.58-3.29 l h^{-1} kg^{-1}). The enantioselectivity of the kinetic disposition of ASOX in patients with neurocysticercosis was reported by Marques et al. (7) with CL/f values expressed as means (N = 18) ranging from 5.8 l h^{-1} kg^{-1} for (+)-ASOX to 54.01 l h^{-1} kg^{-1} for (-)-ASOX and a mean ratio of 9.2 for the AUC(+)-ASOX/AUC(-)-ASOX. The CL/f values presented in Table 3 are comparable to the values reported by Marques et al. (7).

A combination of drugs is not an ideal situation for the study of kinetic disposition; however, the effects obtained by treatment

of neurocysticercosis with albendazole required the combination of dexamethasone, ranitidine and antiepileptics for most of the patients studied (Table 1). It is worth mentioning that the volunteers selected constituted a group representative of patients with neurocysticercosis treated with albendazole. Total antipyrine clearance and clearance for the production of the HMA, NORA and OHA metabolites are selectively influenced by combined drugs. Ranitidine does not impair oxidative or conjugative antipyrine metabolism in healthy subjects while cimetidine reduces antipyrine clearance and the amount of drug absorbed from the gut (26-28). Among the drugs used in combination during the study period, phenytoin and carbamazepine are inducers of CYP2C and CYP3A and are responsible for an increase in total antipyrine clearance and clearance for production of HMA and OHA. Phenytoin appears to be a more powerful inducer of hepatic enzyme activity; total antipyrine clearance increased on average by 91% after phenytoin dosing and by 61% after carbamazepine in male volunteers (29-32). The total antipyrine clearance and clearance for production of metabolites observed for the population studied (Table 2) were considerably higher than those reported for different populations including patients treated with antiepileptics such as phenytoin and/or carbamazepine (22,27). It should be emphasized, however, that dexamethasone, an inducer of CYP3A4 (33,34), is able to potentially induce the formation of OHA and, consequently, to increase total antipyrine clearance. McCune et al. (34) reported that dexamethasone at clinically used doses increased CYP3A4 activity with extensive intersubject variability in healthy volunteers.

Rolin et al. (4), using microsomal preparations of human liver biopsies or cultured human hepatoma cell lines, demonstrated that ASOX and, to a lesser extent, ASON, are potent inducers of CYP and glucuronyltransferase. Steiger et al. (11) investigated patients with echinococcosis and demonstrated that albendazole induces its own metabolism.

Since no data on the isoform(s) of CYP involved in the metabolism of ASOX to

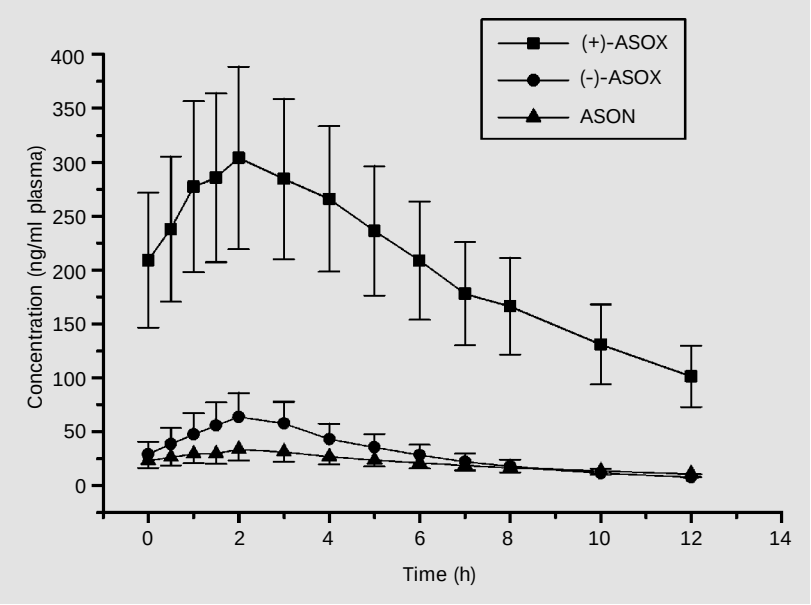

Figure 2. Plasma concentration-time curves of (+)-ASOX, (-)-ASOX and ASON. Data are reported as mean ± SEM (N = 11). ASOX = albendazole sulfoxide; ASON = albendazole sulfone.

Table 4. Orthogonal regression equations and correlation coefficients for clearances between albendazole and antipyrine metabolites (N = 11).

CL/fm	CL_T antipyrine	CL_m HMA	CL_m NORA	CL_m OHA
(+)-ASOX	0.0913 + 0.0247 x r = 0.4987	0.0196 + 0.0048 x r = 0.3475	0.0316 - 0.0003 x r = -0.0028	0.0597 - 0.0018 x r = -0.1953
(-)-ASOX	0.1192 + 0.0021 x r = 0.4369	0.0225+ 0.0005 x r = 0.3235	0.0103 + 0.0004 x r = -0.0090	0.0593 + 0.0002 x r = -0.2487
ASON	0.0645 + 0.0029 x r = 0.6651*	0.0209 + 0.0004 x r = 0.3764	0.0202 + 0.0002 x r = -0.1012	0.0507 + 0.0000 x r = -0.1462

CL/fm = apparent clearance, where fm represents the fraction of the albendazole dose that reached the systemic circulation as a metabolite; CL_T = total clearance; CL_m = clearance for metabolite production. ASOX = albendazole sulfoxide; ASON = albendazole sulfone.

$y = a + bx$, where $b = Syy - Sxx + [(Syy - Sxx)^2 + 4Sxy^2]^{1/2}/2Sxy$ and $a = y - b \times (20)$. r = correlation coefficient; *correlation at the 5% level ($P \leq 0.05$).

ASON in man are available, the results presented here suggest the involvement of the same or similar enzymes in the oxidation of antipyrine and ASOX. Since total antipyrine clearance can be used as a general measure of CYP but with a weight toward CYP1A2 (14), it is suggested that this isoform is involved in the metabolism of ASOX to ASON in man. However, other studies using specific CYP1A2 marker drugs such as caffeine (21) are necessary. In the present study, the major advantage of antipyrine as a multifunctional substrate was to provide a specific marker drug for future contributions related to CYP isoforms involved in the metabolism of ASOX to ASON in man. Multiple drug therapy is a common therapeutic practice in patients with neurocysticercosis treated with albendazole. Thus, careful evaluation of the potential drug interactions based on CYP isoforms is essential.

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