Albendazole Sulfoxide Plasma Levels and Efficacy of Antiparasitic Treatment in Patients With Parenchymal Neurocysticercosis

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Background. The efficacy of albendazole therapy in patients with parenchymal neurocysticercosis (NCC) is suboptimal. Plasma levels of albendazole sulfoxide (ASOX), the active metabolite of albendazole, are highly variable among patients. We hypothesized that high ASOX plasma levels during albendazole therapy may be associated with an increased antiparasitic efficacy.

Methods. ASOX plasma levels were measured at treatment day 7 in 118 patients with parenchymal NCC enrolled in a treatment trial. The relationships between increasing ASOX plasma levels with the proportion of cysts resolved and the proportion of patients with complete cyst resolution (evaluated by 6-month brain magnetic resonance) were assessed.

Results. There was a trend toward a higher proportion of cysts resolved and a higher proportion of patients cured with increasing quartiles of ASOX plasma levels. In patients with 3 or more brain cysts, the regression analysis adjusted by the concomitant administration of praziquantel (PZQ) showed a 2-fold increase in the proportion of cysts resolved (risk ratio [RR], 1.98; 95% confidence interval [CI], 1.01–3.89; $P = .048$) and 2.5-fold increase in the proportion of patients cured (RR, 2.45; 95% CI, .94–6.36; $P = .067$) when ASOX levels in the highest vs the lowest quartile were compared. No association was found in patients with 1–2 brain cysts.

Conclusions. We suggest an association between high ASOX plasma levels and increased antiparasitic efficacy in patients with parenchymal NCC. Nonetheless, this association is also influenced by other factors including parasite burden and concomitant administration of PZQ. These findings may serve to individualize and/or adjust therapy schemes to avoid treatment failure.

Keywords. albendazole; albendazole sulfoxide; praziquantel; neurocysticercosis.

Neurocysticercosis (NCC) is a neurological disease of humans caused by the infection of the central nervous system (CNS) with the larval form (cysticercus) of the pork tapeworm *Taenia solium* [1]. NCC continues to be the leading cause of human acquired epilepsy in most developing countries [2, 3] and is also increasingly diagnosed in nonendemic countries because of travel and immigration of tapeworm carriers from endemic areas [4, 5]. NCC is a major contributor to the global burden of parasitic zoonosis in the world [6]. Hospital charges associated with NCC in the United States account for more than \$908

million [7], while in India NCC results in 1.74 disability-adjusted life years per thousand persons per year [8].

Medical treatment of human NCC with albendazole (ABZ) or praziquantel (PZQ) destroys viable cysts in the brain parenchyma [9, 10], and cyst clearance results in a better clinical prognosis [11, 12]. These drugs have different mechanisms of action. PZQ is a pyrazinoisoquinoline derivate that penetrates the parasite tegument and causes muscular paralysis and tegumentary damage [13], whereas ABZ is a broad-spectrum benzimidazole anthelmintic that causes selective degradation of parasite microtubules, impaired glucose uptake, and reduced parasite survival [14]. ABZ is considered the drug of choice for the treatment of NCC because of its widespread availability and low cost. ABZ has also been shown to be more effective than PZQ [15], probably because ABZ penetrates into the CNS more efficiently [16, 17]. Nonetheless, the effectiveness of these drugs as single antiparasitic agents is only partial, with approximately 60% of parasites destroyed and only 35% of patients being free of surviving cysts after a first round of treatment [9, 10].

After ingestion, ABZ is rapidly oxidized to albendazole sulfoxide (ASOX), the active metabolite responsible for the

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anthelmintic activity [18]. ASOX plasma levels are markedly variable between NCC patients, with percentages of drug bioavailability ranging from 28% to 100% [19]. The pharmacokinetics of ASOX in plasma can also be affected by other factors including concomitant medication. A study by our group demonstrated that ASOX plasma levels were up to 50% higher in NCC patients who received combined therapy with ABZ plus PZQ compared to those who received ABZ alone [20]. Two subsequent studies in patients with parenchymal NCC consistently confirmed the higher antiparasitic efficacy of the combined regimen vs standard or increased-dose ABZ monotherapy [21, 22]. Other factors that affect ASOX levels include concomitant use of steroids, histamine H2 antagonists, and antiepileptic drugs [18, 19]. Under the hypothesis that high ASOX plasma levels during ABZ therapy should increase CNS penetration and contribute to a stronger cysticidal effect, we assessed the relationship between ASOX plasma levels and antiparasitic treatment efficacy in patients with parenchymal NCC.

METHODS

Study Design and Samples

In a double-blind, phase 3 trial of antiparasitic efficacy [21], 118 patients with parenchymal NCC were randomly assigned to receive a 10-day regimen of standard ABZ (15 mg/kg/d, up to 800 mg/d), increased ABZ (22.5 mg/kg/d, up to 1200 mg/d), or combined ABZ (15 mg/kg/d, up to 800 mg/d) plus PZQ (50 mg/kg/d, up to 3600 mg/d). Two blood samples were collected from patients in heparinized tubes 2 and 2.5 hours after their morning dose at treatment day 7 to estimate peak ASOX plasma levels at steady state. Immediately after collection, blood samples were centrifuged at 1200 g for 15 minutes, and plasma aliquots were separated and stored at -80°C until analysis.

Determination of ASOX Plasma Levels

Plasma samples were processed at the Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Brazil, with a previously validated analytical method using high-performance liquid chromatography coupled to mass spectrometry [23] (see details in the [Supplementary Materials](#)). The highest measurement obtained from the 2 plasma samples of patients was taken as the ASOX maximum concentration (C_{max}).

Antiparasitic Treatment Efficacy

Each individual viable cyst was identified on baseline magnetic resonance imaging (MRI), and its stage in follow-up MRI (6 months after treatment) was assessed in order to determine whether the specific cyst had resolved or not. No standard definition of cyst resolution exists. We defined the absence of discernible liquid contents (hyperintense contents on T2 MRI) as a very conservative criterion to define cyst resolution [21, 22]. Lesions with T2-hyperintense cystic contents were deemed

viable cysts regardless of the presence or degree of perilesional edema. Two outcomes were considered to assess treatment efficacy. The main outcome was the proportion of baseline brain cysts resolved after treatment, and the second outcome was the proportion of patients with complete cyst clearance. Outcome assessments were performed blinded to treatment scheme.

Statistical Analyses

ASOX plasma levels as well as demographic and radiological profiles in the patient cohort were summarized using descriptive statistics. Bivariate comparisons between ASOX plasma levels and treatment scheme, antiepileptic drug used, age (divided into 3 categories using terciles), and sex were performed using nonparametric statistical tests (Mann-Whitney *U* for 2 groups and Kruskal-Wallis for multiple groups). The overall correlation between ASOX plasma levels and the total dose/day of ABZ per patient was calculated using the Spearman rank test. ASOX plasma levels were categorized into quartiles according to the overall distribution of ASOX plasma levels in patients. The overall trend of the proportion of cysts resolved and the proportion of patients cured according to increasing quartiles of ASOX levels was assessed. We also performed generalized linear model regression with a modified Poisson approach [24] to estimate risk ratios (RRs) of the relationship between increasing quartiles of ASOX levels with the proportion of cysts resolved (model 1) and the proportion of patients cured (model 2), using the first quartile as the reference level. We used robust variances in models 1 and 2 to correct the overdispersion in the Poisson coefficient estimates for a binomial outcome [24] and also in model 1 to account for the correlation between baseline cysts and cysts resolved in the same patient. Models were stratified by CNS parasite burden (1–2 cysts and 3 or more cysts) and controlled by concomitant administration of PZQ. Statistical analyses were carried out in Stata/IC 15.0 (StataCorp, College Station, TX) using a significance level set to 5%. RRs are presented with their corresponding 95% confidence intervals (CIs).

Ethics Approval

The Universidad Peruana Cayetano Heredia Institutional Review Board approved all the procedures described here (51070, FWA 00002541) as part of the protocol of the primary study.

RESULTS

Demographic and radiological data of the patient cohort have been published elsewhere [21]. There were 118 patients with plasma samples analyzed at treatment day 7 and with 6-month brain MRI efficacy assessment available. Patients had a mean age of 34.2 years (standard deviation [SD], 12.9; range 16–68), 75 (64%) were male, and 43 (36%) were female. Fifty-eight (49%) patients were taking carbamazepine and 60 (51%) were taking phenytoin. The number of brain cysts on basal MRI

ranged from 1 to 20 (median 3 cysts); 56 (47%) patients had 1–2 cysts, and 62 (53%) had 3 or more cysts. Forty-one (35%) patients received the standard ABZ dose, 39 (33%) received an increased ABZ dose, and 38 (32%) received the combined standard ABZ plus PZQ.

As expected, ASOX plasma levels were highly variable among patients (mean 523.2 ng/mL, median 414.3 ng/mL, range 87.7–2166.9 ng/mL). According to treatment scheme, ASOX plasma levels were significantly increased by approximately 50% in the combined ABZ plus PZQ group and in the higher-dose ABZ group compared to the standard-dose ABZ group (overall $P < .001$), whereas drug levels in the combined ABZ plus PZQ group and in the higher dose ABZ group were statistically similar ($P = .488$; Table 1). ASOX plasma levels were marginally higher in patients who were taking carbamazepine compared to those who were taking phenytoin (mean 565.5 ng/mL, median 450.8 ng/mL, range 112.5–2166.9 ng/mL vs mean 482.4 ng/mL, median 379.2 ng/mL, range 87.7–1924.6 ng/mL, $P = .098$). ASOX levels were higher in the first age tercile (mean 566.9 ng/mL, median 436.6 ng/mL, range 114–1368 ng/mL) than in the second and third age terciles (mean 551 ng/mL, median 418.8 ng/mL, range 130.8–2166.9 ng/mL, and mean 446.4 ng/mL, median 354.1 ng/mL, range 87.7–1924.6 ng/mL, respectively), although not statistically different ($P = .181$). Similarly, ASOX levels were not statistically different by sex (mean 505.2 ng/mL, median 413.5 ng/mL, range 87.7–2166.9 ng/mL for males, and mean 533.6 ng/mL, median 415 ng/mL, range 113.4–1924.6 ng/mL for females; $P = .601$; Table 1). The overall correlation between ASOX plasma levels and the

total ABZ dose per patient was significant but low (Spearman $\rho = 0.26$, $P = .004$). Subanalysis in patients who received ABZ alone (either standard or increased-dose regimens) showed an increased correlation (Spearman $\rho = 0.42$, $P < .001$), whereas no correlation was found in patients who also received PZQ (Spearman $\rho = 0.23$, $P = .165$).

We categorized ASOX plasma levels into the following quartiles: 1 (≤ 260.9 ng/mL), 2 (> 260.9 ng/mL to ≤ 413.5 ng/mL), 3 (> 413.5 ng/mL to ≤ 655 ng/mL), and 4 (> 655 ng/mL). A significant trend toward a higher proportion of cysts resolved with increasing quartiles of ASOX plasma levels was found (47.7% [71/149], 56.9% [74/130], 59.2% [84/142], and 77.4% [82/106] for ASOX quartiles 1, 2, 3, and 4, respectively; P for trend $< .001$). Stratified analysis in patients with 3 or more baseline brain cysts corroborated this trend (P for trend $< .001$), and the regression analysis adjusted by concomitant administration of PZQ showed a statistically significant 2-fold increase in the proportion of cysts resolved when comparing ASOX levels in the highest vs the lowest quartile (RR, 1.98; 95% CI, 1.01–3.89; $P = .048$; Table 2). In patients with 1–2 brain cysts, the proportions of cysts resolved were similar among quartiles of ASOX levels (P for trend = .760).

The proportion of patients with complete cyst clearance was also higher with increasing quartiles of ASOX plasma levels, although this did not reach statistical significance (40% [12/30], 48.3% [14/29], 50% [15/30], and 65.5% [19/29] for quartiles 1, 2, 3, and 4, respectively; P for trend = .059). This trend was observed in patients with 3 or more brain cysts ($P = .164$), and the magnitude of the association was marginally higher when

Table 1. Albendazole Sulfoxide Plasma Levels According to Demographic and Treatment Profiles in Patients With Parenchymal Neurocysticercosis (n = 118)

Characteristics	Albendazole Sulfoxide Plasma Level (ng/mL)			PValue
	Mean	Median	Range	
Age terciles (y)				
16–26	566.9	436.6	114.0–1368.0	.181 ^a
27–38	551.8	418.8	130.8–2166.9	
39–68	446.4	354.1	87.7–1924.6	
Sex				
Female	505.2	413.5	87.7–2166.9	.601 ^b
Male	533.6	415.0	113.4–1924.6	
Antiepileptic drug				
Carbamazepine	565.5	450.8	112.5–2166.9	.098 ^b
Phenytoin	482.4	379.2	87.7–1924.6	
Therapy scheme ^c				
Standard ABZ	390.5	271.9	87.7–1280.7	.001 ^a
Increased ABZ	584.3	535.2	194.0–1364.6	
Combined ABZ plus praziquantel	603.3	449.3	183.7–2166.9	

Abbreviation: ABZ, albendazole.

^aP value for Kruskal-Wallis test.

^bP value for Mann-Whitney *U* test.

^cStandard ABZ (15 mg/kg/d, up to 800 mg/d), increased ABZ (22.5 mg/kg/d, up to 1200 mg/d), and combined ABZ (15 mg/kg/d, up to 800 mg/d) plus praziquantel (50 mg/kg/d, up to 3600 mg/d).

Table 2. Adjusted Risk Ratios for the Proportion of Cysts Resolved and the Proportion of Patients Cured According to Increasing Quartiles of Albendazole Sulfoxide Levels in Patients With Parenchymal Neurocysticercosis

Albendazole Sulfoxide Plasma Level ^a	Cysts Resolved			Patients Cured		
	Cysts Resolved/Baseline Cysts (%)	ARR (95% CI)	PValue	n/N (%)	ARR (95% CI)	PValue
1–2 brain cysts						
Q1	9/13 (69.2)	Ref.	Ref.	8/12 (66.7)	Ref.	Ref.
Q2	9/12 (75.0)	1.03 (.59–1.82)	.914	9/12 (75.0)	1.18 (.69–2.02)	.536
Q3	13/19 (68.4)	1.29 (.74–2.26)	.366	9/14 (64.3)	1.04 (.59–1.82)	.904
Q4	18/22 (81.8)	1.40 (.82–2.37)	.217	14/18 (77.8)	1.26 (.78–2.02)	.344
3 or more brain cysts						
Q1	62/136 (45.6)	Ref.	Ref.	4/18 (22.2)	Ref.	Ref.
Q2	65/118 (55.1)	1.26 (.66–2.41)	.482	5/17 (29.4)	1.53 (.64–3.66)	.343
Q3	71/123 (58.7)	1.43 (.80–2.53)	.225	6/16 (37.5)	1.89 (.75–4.75)	.175
Q4	64/84 (76.2)	1.98 (1.01–3.89)	.048	5/11 (45.5)	2.45 (.94–6.36)	.067

Risk ratios calculated from generalized linear models adjusted by concomitant administration of praziquantel and stratified by central nervous system parasite burden.

Abbreviations: ARR, adjusted risk ratio; CI, confidence interval.

^aAlbendazole sulfoxide quartiles: Q1 (≤ 260.9 ng/mL), Q2 (>260.9 ng/mL to ≤ 413.5 ng/mL), Q3 (>413.5 ng/mL to ≤ 655 ng/mL), and Q4 (>655 ng/mL).

patients with ASOX levels in the highest quartile were compared to those in the lowest quartile (RR, 2.45; 95% CI, .94–6.36; $P = .067$; Table 2). In patients with 1–2 brain cysts, there were no differences in cure rates between quartiles of ASOX levels (P for trend = .632).

Concomitant administration of PZQ was independently associated with a higher proportion of cysts resolved (59.1% [177/198] vs 40.7% [134/329]; $P < .001$) and a higher proportion of patients cured (64.1% [25/39] vs 44.3% [35/79]; $P = .043$). Stratified analysis showed a marked effect in patients with 3 or more brain cysts (RR, 3.48; 95% CI, 2.15–5.64; $P < .001$ for the proportion of cysts resolved and RR, 4.12; 95% CI, 1.99–8.50; $P < .001$ for the proportion of patients cured, respectively), whereas no effect was observed in patients with 1–2 cysts.

DISCUSSION

Therapy of viable parenchymal brain cysticercosis involves the use of antiparasitic agents, most frequently ABZ [12, 25], although its effectiveness is partial, resolving fewer than two thirds of cysts and clearing all cysts in approximately one third of patients [9, 10]. Our findings reported here suggest a direct relationship between higher ASOX plasma levels and increased antiparasitic treatment efficacy. This association was also affected by other factors including parasite burden in the CNS and concomitant administration of PZQ. Taken together, these findings may serve to individualize and/or adjust therapy schemes in patients with parenchymal NCC to improve their prognosis and to avoid treatment failure.

The antiparasitic efficacy of ABZ is closely related to the bioavailability of its active compound, ASOX [18]. After ingestion, ABZ is rapidly oxidized to ASOX by flavin mono-oxygenases and CYP450 enzymes, mainly CYP3A4 [18]. In this form, the drug passes through the blood–brain barrier and reaches the

CNS where it exerts its therapeutic effect, so that the amount of ASOX in the cerebrospinal fluid is probably the main determinant of its efficacy in the treatment of NCC. Given the high correlation between ASOX levels in plasma and cerebrospinal fluid [26], monitoring ASOX plasma levels in patients during ABZ therapy may reflect the amount of the drug in the CNS.

ASOX plasma levels in patients may be increased either by increasing the dose of ABZ or by combining it with PZQ. Our data showed statistically higher ASOX levels in patients in the higher-dose ABZ group vs those in the standard-dose ABZ group, which confirms the dose-dependent ABZ pharmacokinetics after oral ingestion [27, 28]. Nonetheless, drug levels were also higher in the combined ABZ plus PZQ group. Previous studies conducted in healthy volunteers [29, 30] and in NCC patients [20] demonstrated that concomitant PZQ administration alters the pharmacokinetics of ASOX and therefore its bioavailability. Our findings also suggest an independent effect of concomitant PZQ administration on ASOX plasma levels, as ASOX plasma levels are correlated with the total ABZ dose in the subgroup of patients who received ABZ alone, but this correlation disappears and efficacy increases in those who also received PZQ. The exact mechanism of this potential interaction is not known. However, since enzymatic induction involved in ABZ oxidation does not seem to occur as a result of single-dose PZQ administration [30], it has been suggested that PZQ acts as an inhibitor of P-glycoprotein, an efflux protein that limits the cellular intake of drugs and metabolites from the intestinal lumen to the epithelial cells [31] and from blood circulation into the CNS due to its high distribution in the capillary endothelial cells that make up the blood–brain barrier [32]. Two studies, one showing the in vitro inhibitory effect of PZQ on P-glycoprotein but not on its substrate in Caco-2 cells [33] and the other showing PZQ resistance associated with expression of P-glycoprotein-like transporter SMDR2 in experimental

Schistosoma mansoni infections in mice [34], support the role of this protein in pharmacokinetics and drug interactions.

Other factors may also be related to the high interindividual variability of ASOX plasma levels. Although not statistically significant, a trend toward lower ASOX levels with increasing age tertiles in patients was found. No data regarding the effect of age on ASOX pharmacokinetics in humans exist. Nonetheless, aging has a negative impact on hepatic function, specifically in the induction of most CYP enzymes involved in drug metabolism [35, 36]. ASOX plasma levels were similar in male and female patients, in contrast to previous studies that suggest sexual dimorphism in the pharmacokinetics of ABZ due to a female-dominant expression of CYP3A4, the main enzyme involved in ABZ oxidation [37, 38]. We observed higher ASOX levels in patients who were taking carbamazepine vs those who were taking phenytoin. Antiepileptic drugs are known to be potent inducers of CYP enzymes, mostly CYP3A4, CYP2C9, and CYP219 [39], and the results of 2 previous studies indicate that the effect of carbamazepine and phenytoin on ABZ metabolism is similar [20, 40]. Patients who received carbamazepine were, on average, younger than those who received phenytoin (mean, 31.8 years [SD, 12.9; range, 16–68] vs mean 36.5 years [SD, 12.5; range, 17–63], respectively, not reported in the results section), which may explain the marginal differences in ASOX plasma levels according to the antiepileptic drug used. Additionally, all patients in the cohort received antiinflammatory therapy with dexamethasone, which has been reported to decrease the elimination rates of ASOX and thus alter its pharmacokinetics [41, 42].

Our findings suggest a direct relationship between ASOX plasma levels and antiparasitic efficacy in patients with parenchymal NCC. Stratified analysis according to CNS parasite burden showed a marked effect in patients with 3 or more brain cysts but no effect in patients with only 1–2 cysts. Cysticidal therapy has been demonstrated to be more effective in patients

with multiple parenchymal cysts, as reported in the primary study [21] and confirmed in a subsequent study [22]. The death of cysts in the CNS after treatment does not occur immediately but results from the impact of the host immune response on damaged cysts [43]. One explanation for our findings is that cyst damage due to antiparasitic treatment induces the release of antigens and activates the host's immune response to further attack and destroy other larvae in the brain parenchyma, resulting in inflammation (Figure 1) [43]. Therefore, a greater amount of antigen released in multiple infections compared to single infections may trigger a stronger immune response. In this context, higher ASOX plasma levels may account for the increased cyst damage and antigen exposure that boosts cyst destruction by the host immune system. PZQ also has a direct cysticidal effect due to the damage that it causes in the parasite tegument [13]. Thus, the addition of PZQ into the ABZ treatment scheme, in addition to increasing ASOX plasma levels, may also contribute to the production of more cyst damage and antigen release.

Our study has some limitations. Since the study was powered for cysticidal efficacy and not for plasma level analyses, the presence of marginal associations may represent the lack of statistical power for the comparisons. In addition, we used the highest ASOX level from 2 plasma samples taken 2 and 2.5 hours after their morning dose at treatment day 7 to approximate Cmax [20]. Some patients may have reached Cmax outside the period of sampling. Additionally, we only estimated ASOX Cmax values to assess the relationship between drug levels and antiparasitic efficacy. Cmax values only represent the rate of absorption of a drug, whereas the area under the plasma drug concentration-time curve (AUC) would have provided a more reliable measure of the extent of drug exposure following a dose. However, accurate measurement of AUC values would be impossible in a large number of patients, so ASOX Cmax values at day 7 (steady state) may be a suitable surrogate measure to

Figure 1. Brain magnetic resonance imaging fluid-attenuated inversion recovery of a patient with multiple parenchymal cysts before and after antiparasitic treatment. *A*, Viable parenchymal brain cysts (white arrows) at baseline. *B*, Markedly degenerated cysts (black arrows) surrounded by inflammation 30 days after antiparasitic treatment.

guide treatment. Finally, PZQ plasma levels were not measured in this study since the primary study was designed to evaluate the anthelmintic efficacy of ABZ in 3 regimens (only 38 of 118 patients [32.2%] received PZQ).

NCC continues to be a major cause of neurological disease in most of the world, and incomplete cyst resolution leads to prolonged disease that requires continued surveillance with repeated expensive and poorly available neuroimaging, as well as subsequent courses of anthelmintic treatment. A more effective treatment would greatly reduce costs and may result in improved clinical evolution. Our study suggests that monitoring of ASOX plasma levels during ABZ therapy can be a useful tool to improve ABZ therapy in patients with multiple parenchymal NCC and to confirm the potential effect of combined ABZ plus PZQ therapy in increasing ASOX plasma levels and increased antiparasitic efficacy. Monitoring ASOX levels (eg, Cmax at day 7) and adjusting the dosage in patients with sub-optimal drug exposure (either by increasing the ABZ dose or combining ABZ with PZQ) might improve treatment outcomes in parenchymal NCC.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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