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MAJOR ARTICLE

Cysticidal Efficacy of Combined Treatment With Praziquantel and Albendazole for Parenchymal Brain Cysticercosis

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Background. The efficacy of current antiparasitic treatment for cerebral *Taenia solium* cysticercosis with either albendazole (ABZ) or praziquantel (PZQ) is suboptimal. A recent study demonstrated that combining these 2 antiparasitic drugs improves antiparasitic efficacy. We present here the parasiticidal efficacy data obtained during a previous phase II pharmacokinetic study that compared combined ABZ plus PZQ with ABZ alone.

Methods. The study was a randomized, double-blinded, placebo-controlled phase II evaluation of the pharmacokinetics of ABZ (15 mg/k/d, for 10 days) and PZQ (50 mg/k/d, for 10 days) in intraparenchymal brain cysticercosis. Patients received the usual concomitant medications, including an antiepileptic drug (phenytoin or carbamazepine), dexamethasone, and ranitidine. Randomization was stratified by antiepileptic drug. Patients underwent safety laboratory evaluations at days 4, 7, and 11, as well as magnetic resonance (MR) imaging at 6 months to assess parasiticidal efficacy.

Results. Thirty-two patients were included, 16 in each arm. All of them completed antiparasitic treatment and underwent follow-up brain MR imaging. Cysticidal efficacy was strikingly higher in the combined ABZ-plus-PZQ group than in the ABZ-alone group (proportion of cysts resolved, 78 of 82 [95%] vs 23 of 77 [30%] [relative risk {RR}, 3.18; 95% confidence interval {CI}, 2.08–4.88; $P < .001$]; patients with complete cyst clearance, 12 of 16 [75%] vs 4 of 16 [25%] [RR, 3.00; 95% CI, 1.23–7.34; $P = .005$]).

Conclusions. The combination of ABZ plus PZQ is more effective in destroying viable brain cysticercosis cysts than ABZ alone.

Clinical Trials Registration. NCT00441285.

Keywords. albendazole; praziquantel; neurocysticercosis; *Taenia solium*; Peru.

The cystic larvae of the pork tapeworm *Taenia solium* frequently affect the human brain causing neurological symptoms, particularly late-onset seizures and epilepsy [1]. This condition, neurocysticercosis (NCC), is a major cause of seizures worldwide [2]. Currently, most experts agree that antiparasitic treatment of viable brain cysts (in addition to symptomatic therapy with analgesics, antiepileptic drugs, and anti-inflammatory agents, such as steroids) is indicated to reduce the likelihood of further seizure episodes, as well as to minimize the risks of disease progression [3–6].

Specific antiparasitic treatment uses either praziquantel (PZQ, 50 mg/k/d for 15 days), or albendazole (ABZ, 15 mg/k/d for 8–30 days) [3, 4, 7, 8]. However, the parasiticidal efficacy of an initial course of either agent only decreases the number of viable parasites by about 60%–70%, Furthermore, only 30%–40% of patients achieve complete parasite clearance after a first course of antiparasitic treatment [7, 8].

ABZ and PZQ have different mechanisms of action [9, 10]. We hypothesized that combining ABZ and PZQ should result in improved parasiticidal efficacy, and therefore performed an initial phase II study of pharmacokinetics and preliminary safety. Pharmacokinetic data demonstrated a 48% increase in ABZ serum levels when given in combination with PZQ [11]. On the recommendation of the study Data and Safety Monitoring Board (DSMB), the efficacy data from this preliminary study was kept blinded, and a phase III study was performed, including an additional arm with an increased ABZ dose, which demonstrated increased efficacy of combined antiparasitic therapy in patients with multiple cysts [5]. We present here the parasiticidal efficacy data from the initial phase II study, which are largely concordant with the findings of the published phase III trial.

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METHODS

Study Design

Details of the study design and methods have already been published when the pharmacokinetic data were reported [11]. In short, this was a randomized, double-blinded, placebo-controlled phase II pharmacokinetics study comparing ABZ treatment with and without PZQ in patients with NCC, given with all other usual concomitant medications. Patients were enrolled at a neurological hospital (Cysticercosis Unit, Instituto Nacional de Ciencias Neurologicas, Lima, Peru), from August 2007 to June 2008. The study was registered at ClinicalTrials.gov with identifier NCT00441285. Subjects included were aged 16–65 years and had parenchymal brain cysticercosis with ≤20 viable cysts and a diagnosis of epilepsy secondary to NCC. Other criteria for inclusion were positive serological findings for cysticercosis; willingness to complete ≥2 weeks of hospitalization; adequate contraception; normal laboratory values for hematocrit, platelet and white blood cell counts, and glucose, liver enzyme, and creatinine levels; negative tuberculosis skin test results or, if positive, negative smears for tuberculosis; negative results of fecal examinations for *Taenia* eggs or *Strongyloides* larvae; and treatment with a stable monotherapy regimen of phenytoin or carbamazepine for ≥15 days. Consenting patients provided a complete history and underwent physical examination, including eye fundus examination, electroencephalography, and brain computed tomography and magnetic resonance (MR) imaging [11].

Exclusion criteria included primary generalized seizures; history of generalized status epilepticus; subarachnoid cysts in the Sylvian fissure or basal cisterns, except for cysts in the Sylvian fissure substantially surrounded by brain parenchyma; intraventricular cysts; cysts in the brain stem; cysts >2.5 cm in mean diameter; untreated ocular cysticercosis; persistent or progressive symptomatic intracranial hypertension or intracranial hypertension defined radiologically; treatment with ABZ or PZQ in the past 2 years (except in patients receiving ≤1200 mg of ABZ with a further evaluation demonstrating continued viability of cysts; pulmonary tuberculosis or symptoms compatible with tuberculosis (fever with sweats or fever with cough) not otherwise explained; active hepatitis; known systemic disease; unstable condition; hypersensitivity to ABZ or PZQ; concurrent treatment with cimetidine or theophylline; chronic alcohol or drug abuse; and inability or unwillingness to undergo follow-up computed tomography or MR imaging or to give written informed consent.

Randomization was done in blocks of size 4 and 6 and stratified by antiepileptic drug (carbamazepine or phenytoin). Study drugs were placed in sealed, labeled envelopes, one for PZQ or placebo (containing PZQ in 16 cases and placebo in the remaining 16), and one for ABZ (containing active drug for all patients).

The intervention regimens used PZQ at 50 mg/k/d, up to 3600 mg/d, as an add-on to ABZ treatment at 15 mg/k/d, up to 800 mg/d, both for 9½ days. The second dose on treatment day 10 was not included to allow pharmacokinetic steady state sampling to occur during the day rather than at night. The comparison group received the same standard ABZ regimen and PZQ placebo. Drugs were administered in the hospital by a study nurse. Additional concomitant medication included appropriate doses of phenytoin or carbamazepine, dexamethasone at 0.1 mg/k/d, divided into 2 doses (morning and evening), and 300 mg/d of ranitidine (Figure 1).

Efficacy Assessment

The study team identified each individual cyst in the baseline, pretreatment MR imaging study and recorded the characteristics in terms of location, appearance, size, and presence of perilesional signs of inflammation. Follow-up MR imaging was performed 6 months after treatment onset and patients with persisting viable parasites were offered a second course of antiparasitic treatment. Outcome assessment was performed with blinding to treatment arm. Once the study team was permitted to visualize the follow-up MR images by the study DSMB, they determined whether each specific cyst had resolved or not. The study statistician then assembled a database linking MR images and treatment arms and proceeded to the analysis.

Working Definitions

Viable Cyst

A viable cyst was defined as one alive and capable of develop into an adult tapeworm. On the basis of studies in pigs and human pathology samples, a cyst was considered viable if the cyst fluid was present and appeared similar cerebrospinal fluid on MR images (hypointense using T1 and fluid-attenuated inversion recovery protocols, hyperintense using a T2 protocol).

Complete Cyst Resolution

Absence of discernible liquid contents (no hyperintense signal in cyst contents using the T2 protocol) was used as a very conservative criterion to define cyst resolution.

Statistical Analysis

Differences in proportions between groups were assessed using χ^2 or Fisher exact tests. Differences in continuous variables were assessed with Student *t* or Mann–Whitney's tests. Parasiticidal efficacy was expressed as both the proportion of cysts resolved and the proportion of patients with complete cyst clearance. Comparisons of the proportions of cysts resolved used a generalized linear model with robust estimates of standard errors to account for the correlation between cysts in the same patient.

Human Subject Protection

The study protocol and informed consents were revised and approved by the main institutional review board of the Universidad Peruana Cayetano Heredia in Lima, Peru (institutional review board code 51070, FWA 00002541). A DSMB established before study initiation revised the protocol and supervised the entire study.

RESULTS

Study Subjects

The study included 21 men and 11 women, with a mean age of 28.4 years (standard deviation, 10.3 years). There were no differences between treatment groups in patient age, sex, height, or weight [11].

Characteristics of Infection at Baseline

Patients had a mean of 5.0 cysts (median, 4.0; interquartile range, 1.0–6.5). We observed no significant differences between groups in terms of overall numbers of cysts (mean, 5.1 per patient in the combined group vs 4.8 in the ABZ group; $P = .59$), patients with 1 or 2 cysts (7 of 16 vs 6 of 16, respectively; $P = .50$), or individual cysts with perilesional edema (16 of 82 vs 25 of 77; $P = .33$).

Parasiticidal Efficacy

Resolution of cysts was much higher in the combination group than in the ABZ-alone group (78 of 82 [95%] vs 23 of 77 [30%], respectively; relative risk [RR], 3.18; 95% confidence interval [CI], 2.08–4.88; $P < .001$). The increased parasiticidal effect of combination therapy was more marked in patients with ≥3 cysts (99% [73 of 74] vs 29% [20 of 68], respectively; RR, 3.35; 95% CI, 2.11–5.34; $P < .001$) than in those with 1 or 2 cysts (63% [5 of 8] vs 33% [3 of 9]; 1.87; .53–6.62; $P = .33$). Similarly, the proportion of patients with complete cyst clearance was also higher in the combination group (12 of 16 [75%] vs 4 of 16 [25%]; RR, 3.00; 95% CI, 1.23–7.34; $P = .005$). There were 9 patients in whom all cysts remained viable, 3 in the combination group (each with a single cyst at baseline) and 6 in the ABZ group (3 patients with 2 cysts and 1 each with 3, 6, and 10 cysts at baseline) (Table 1).

The efficacy of combined therapy was higher in lesions without inflammation (65 of 66 [99%] vs 13 of 16 [81%] in those with inflammation), whereas the efficacy of ABZ alone was higher in lesions with inflammation, evidenced as perilesional edema (14 of 25 cysts [56%] with perilesional edema resolved vs 9 of 52 [18%] without edema). This interaction was statistically significant ($P < .001$).

There were no differences in parasiticidal efficacy by antiepileptic drug, either overall ($P = .99$) or after controlling for PZQ ($P = .97$). The efficacy of combined ABZ plus PZQ was 98% of cysts cleared (39 of 40) in patients taking carbamazepine and 93% (39 of 42) in those taking phenytoin, whereas the efficacy of ABZ alone was 27% (10 of 37) in patients taking carbamazepine and 33% (13 of 40) in those taking phenytoin.

DISCUSSION

Despite the small sample size of this phamacokinetic study, the efficacy outcome in these 32 patients demonstrated a marked and statistically significant parasiticidal superiority of the combination of ABZ plus PZQ compared with ABZ plus placebo. The study was not designed to evaluate efficacy, and thus a further phase III study with an appropriate sample size was later performed and published [12] before this work was submitted for publication. The conclusions from both studies are remarkably consistent.

The death of brain NCC cysts after antiparasitic therapy does not occur immediately but results from the host immune system attacking, infiltrating, and destroying the macroscopic parasite in the brain parenchyma [2, 13]. Thus it seems that antiparasitic medication damages the cysts, exposes antigens, and alters immune evasion mechanisms, allowing the immune system to detect

Table 1. Baseline Group Characteristics and Cysticidal Efficacy of Albendazole (ABZ) Alone and ABZ Plus Praziquantel in Viable Parenchymal Brain Cysticercosis

	ABZ + PZQ (n = 16)	ABZ Alone (n = 16)	*P* Value
Baseline characteristic			
No. of cysts			
Total	82	77	. . .
Mean (SD)	5.13 (5.43)	4.81 (3.51)	.59
Range	1–18	1–12	. . .
Patients with 1–2 cysts, No. (%)	7 (44)[a]	6 (38)[b]	.50
Cysts with perilesional edema, No. (%)	16 (20)	25 (32)	.33
Treatment efficacy			
Cysts resolved, No. (%)	78 (95)	23 (30)	<.001
Patients with complete cyst clearance, No. (%)	12/16 (75)	4/16 (25)	.005
Cysts resolved, No. (%)			
1–2 Cysts on baseline scan	5/8 (63)	3/9 (33)	.33
≥3 Cysts on baseline scan	73/74 (99)	20/68 (29)	<.001
With perilesional edema	13/16 (81)	14/25 (56)	.09
Without perilesional edema	65/66 (98)	9/52 (17)	<.001

Abbreviations: ABZ, albendazole; PZQ, praziquantel; SD, standard deviation.

[a] Eight cysts total.

[b] Nine cysts total.

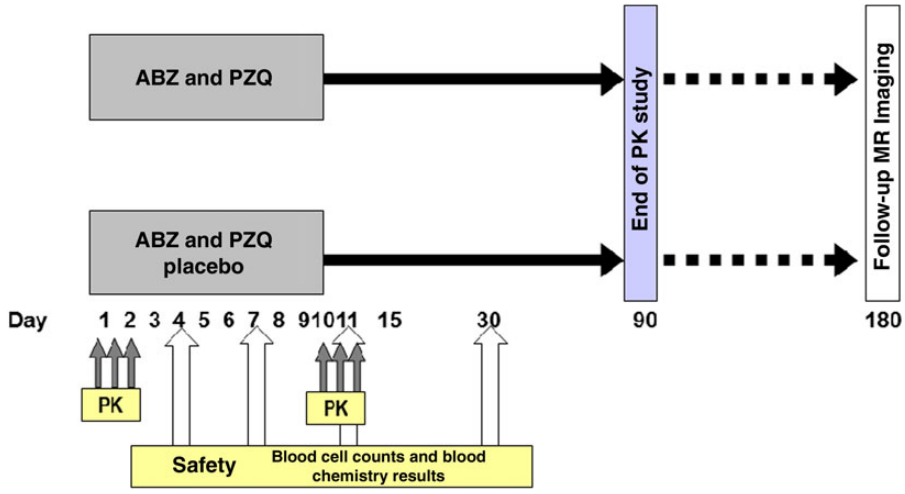

Figure 1. Flowchart of the study demonstrating group allocation (n = 16 per group), sampling and follow-up periods. Abbreviations: ABZ, albendazole; MR, magnetic resonance; PK, pharmacokinetic; PZQ, praziquantel.

and attack the parasite. ABZ is a benzimidazole that acts primarily through selective degeneration of parasite cytoplasmic microtubules, leading to decreased adenosine triphosphate formation and energy depletion [9]. It also binds to tubulin disrupting cell division and affects glucose intake leading to parasite starvation. PZQ is a pyrazinoisoquinoline derivative that causes muscular contraction, paralysis, and tegumentary damage. Other effects of PZQ include changes in carbohydrate metabolism, decrease in enzymatic activities, and alterations in surface membranes [10]. Because the mechanisms of action of these 2 accepted parasiticidal drugs are radically different, it might be expected that a combination would increase the likelihood of exposing antigens to an even greater extent.

The combination of ABZ plus PZQ has been used for geohelminth-schistosomiasis coinfections [14] in larva migrans [15], clonorchiasis [16], and hydatid disease [17, 18]. In areas where schistosomiasis and geohelminths are coendemic, the combination is usually given as a single dose to schoolchildren and others in the community during mass treatment campaigns. In hydatid disease, despite the lack of controlled trials, the combination seems to prevent new infections resulting from cyst content spillage at the time of surgery. There are only 4 reports of the use of the combination in human NCC. In 2003 Guo et al [19] reported increased cysticidal efficacy in a series of 90 patients in China. In 2009 Kaur et al [20] reported a statistically nonsignificant increase in parasiticidal efficacy in 112 Indian children with a single degenerating brain cysticercus. The third and fourth reports are the pharmacokinetics report [11] and the subsequent phase III study [12].

The results of the pharmacokinetic interaction between ABZ and PZQ were published in 2011. The phase III study in 124 patients demonstrated higher efficacy of the ABZ-plus-PZQ combination compared with ABZ alone in either standard (15 mg/kg/d) or higher (22.5 mg/kg/d) doses [5]. The efficacy results of this smaller study confirmed the results of the phase III trial, providing consistent evidence to support the superiority of combined therapy in terms of parasite destruction. Interestingly, the difference in efficacy of combined treatment was again more marked in patients with multiple cysts [5]. The cysticidal efficacy of ABZ alone was similar in this and the phase III study (30% vs 28%). This is lower than previous reports and may result from the more stringent and conservative criteria used for cyst resolution (cysts that showed evident degenerative changes but still had liquid contents were categorized as not resolved), and the ceiling of 800 mg/d as indicated by the US Food and Drug Administration and used in the United States. Latin American centers commonly apply a less conservative ceiling for ABZ of 1200 mg/d.

Our findings confirm that combined therapy has a much higher parasiticidal efficacy against viable cysticerci compared with ABZ monotherapy. The long-term clinical effect of destroying viable brain cysticerci with antiparasitic drugs (ie, evolution of the seizure disorder) is affected by many variables that include the number of cysts, their location in brain areas that are more or less clinically expressive, whether they resolve completely or leave a calcified scar, and probably other clinical variables, such as the previous time with seizures and the number and type of previous seizures. In general, the likelihood of further seizure episodes seems much higher while a parasite is dying and the subsequent inflammatory process (which may continue for a long time) is ongoing, and is reduced again a few years after all parasites have died [3, 7, 21, 22]. The goal of therapy is thus to destroy all parasites to avoid future foci of inflammation. Combining ABZ and PZQ, as a more effective cysticidal treatment, is a step in this direction. The unfinished agenda in the medical treatment of parenchymal NCC still includes better modulation of natural and treatment-induced inflammation and reducing the likelihood of residual calcifications [23].

Notes

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