A Trial of Antiparasitic Treatment to Reduce the Rate of Seizures Due to Cerebral Cysticercosis

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BACKGROUND

Neurocysticercosis is the main cause of adult-onset seizures in the developing world. Whether therapy with antiparasitic agents results in improved seizure control has been questioned because of the lack of adequate, controlled studies.

METHODS

We conducted a double-blind, placebo-controlled trial in which 120 patients who had living cysticerci in the brain and seizures treated with antiepileptic drugs were randomly assigned to receive either 800 mg of albendazole per day and 6 mg of dexamethasone per day for 10 days (60 patients) or two placebos (60 patients). The patients were followed for 30 months or until they had been seizure-free for 6 months after the doses of the antiepileptic drugs had been tapered. The efficacy of treatment was measured as the decrease in the number of seizures after treatment.

RESULTS

In the albendazole group, there was a 46 percent reduction in the number of seizures (95 percent confidence interval, −74 to 83 percent) during months 2 to 30 after treatment. This reduction, which was not statistically significant, was composed of a non-significant reduction of 41 percent in the number of partial seizures (95 percent confidence interval, −124 to 84 percent) and a significant 67 percent reduction in the number of seizures with generalization (95 percent confidence interval, 20 to 86 percent). Most of the difference in the number of partial seizures was attributable to a few patients who had many seizures during follow-up. The proportions of patients who had partial seizures during follow-up were similar in the two groups (19 of 57 in the albendazole group and 16 of 59 in the placebo group), but the patients in the placebo group had a greater tendency to have seizures with generalization (22 of 59, vs. 13 of 57 in the albendazole group; risk ratio, 1.63; 95 percent confidence interval, 0.91 to 2.92). More of the intracranial cystic lesions resolved in the albendazole group than in the placebo group. With the sole exception of abdominal pain, side effects did not differ significantly between the two groups.

CONCLUSIONS

In patients with seizures due to viable parenchymal cysts, antiparasitic therapy decreases the burden of parasites and is safe and effective, at least in reducing the number of seizures with generalization.

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IN THE DEVELOPING WORLD, NEUROCYSTICERCOSIS — infection of the central nervous system with Taenia solium larvae — is the single most common cause of acquired epilepsy. In Latin America alone, it is estimated that more than 400,000 persons have neurologic symptoms due to neurocysticercosis. The disease has also become increasingly recognized in industrialized countries, because of immigration from countries where the infection is endemic and improved neuroimaging and serologic means of diagnosis. Recently, neurocysticercosis was found in 10 percent of patients with seizures who presented to an emergency department in Los Angeles and 6 percent of such patients in New Mexico.

In the brain, T. solium larvae survive for a poorly defined period, estimated to be several years, and then degenerate into granulomas that in turn become calcified scars (Fig. 1). Infestation of the cerebral parenchyma is usually manifested as seizures and is more frequent than extraparenchymal infestation (involving the ventricles, basal cisterns, or subarachnoid space). The prognosis and management differ considerably according to the location, life-cycle stage, and number of parasites in the central nervous system. Albendazole is the antiparasitic drug of choice; it kills cerebral cysts in humans and in pigs. No double-blind, placebo-controlled trials have yet been performed to test whether the course of seizures associated with viable parenchymal cysts is improved with albendazole therapy. Three major arguments against the use of antiparasitic therapy in neurocysticercosis have been raised: first, that there are immediate risks because of neurologic symptoms due to the acute inflammation that results from the death of the cysts; second, that the long-term prognosis of the underlying seizure disorder may worsen because of increased scarring due to the acute inflammation; and third, that treatment is unnecessary since most cysts die by themselves within a short period. We evaluated the effects of albendazole therapy on seizures in patients with intraparenchymal neurocysticercosis.

METHODS

Between January 1997 and March 1999, 120 adult Peruvian patients with viable parenchymal cysts were consecutively enrolled after their written informed consent had been obtained. Criteria for inclusion were the presence of well-delimited, round, hypodense cysts on cerebral computed tomography (CT), serologic confirmation of T. solium infection by enzyme-linked immuno-electrotransfer blot assay, and a history of one or more spontaneous seizures within the previous 6 months but less than 10 years in duration. Seizures were diagnosed and categorized according to standard criteria from the International League against Epilepsy. Patients were excluded from the study if they had primary generalized seizures, a history of antiparasitic treatment, more than 20 cysts on CT, evidence on CT of other diseases not attributable to cysticercosis, moderate or severe intracranial hypertension, status epilepticus, focal neurologic deficits, unstable vital signs, or an impending risk of death. Patients were also excluded if they were pregnant. The study and the written consent form were approved by the institutional review boards of the Johns Hopkins University Bloomberg School of Public Health in Baltimore and the Universidad Peruana Cayetano Heredia in Lima.

STAGE OF PARASITES

This study included patients with at least one viable cyst, defined as a hypodense vesicle visible on CT. Cysts with signs of inflammation (edema or contrast enhancement) were included only if CT clearly showed that they had liquid contents (as indicated by a density on imaging similar to that of cerebrospinal fluid) and if the presence of liquid was confirmed by magnetic resonance imaging (MRI) (as a hyperintense signal on T2-weighted imaging and a hypointense signal on fluid-attenuation inversion recovery protocols). Lesions with inflammation were considered to be a separate subgroup during analysis, because such lesions represent parasites that have already been attacked by the host’s immune system. Parasites that had already degenerated at the time of a patient’s enrollment (as indicated by the presence of lesions surrounded by edema and showing abnormal enhancement but without discernible liquid contents) were not considered in the evaluation of treatment efficacy.

EXAMINATION AND TREATMENT

All the consenting patients provided a complete history and underwent physical examination, electroencephalography, MRI of the brain, plain-film radiographs of the chest, stool examinations, and hematologic studies, including measurements of glucose and creatinine levels and liver-function tests.
MRI was used to improve the precision of the imaging diagnosis in terms of the number of lesions and their stage and thus to improve the base-line assessment and allow better follow-up comparisons. Eligible patients were then enrolled and assigned a study number. Random assignment of the patients to one of the two study groups was performed (in Lima, by a biostatistician not otherwise involved in the study) in blocks of six according to a preestablished list taken from a random-numbers table.

Patients were admitted to the hospital and received either 400 mg of albendazole given orally every 12 hours and 2 mg of dexamethasone given orally every 8 hours for 10 days or two placebos of similar appearance at the same intervals and for the same period. All drugs and placebos were administered by the study personnel, who received them in sealed, opaque, sequentially numbered envelopes.

Adequate antiepileptic-drug therapy (one first-line antiepileptic drug given at internationally ac-

Figure 1. Stages of Neurocysticercosis Lesions in the Human Brain.
Contrast-enhanced T₁-weighted MRI scans show a viable cyst (Panel A), a cyst with the initial signs of inflammation (Panel B), and a degenerating cyst (Panel C). A CT image obtained without the use of contrast material shows calcified parasites (Panel D).

A B
C D
cepted doses and monitored by measuring its serum level, as prescribed by the patients’ attending neurologist, was provided free of charge. If they were not already receiving treatment, enrolling patients were given phenytoin. If seizure control was poor (i.e., if more than two seizures occurred during a six-month period), patients were interviewed, the blood level of their antiepileptic drug was measured, and the dosage was adjusted if needed. If seizures still remained poorly controlled, therapy was switched to a different antiepileptic drug. After one seizure-free year, the drug dosage was tapered over a two-month period and stopped. Patients left the study if they had had six seizure-free months after the tapering of their antiepileptic drug.

Before discharge, all patients received information regarding indications for therapy, a supply of antiepileptic drugs, and a diary to record any symptoms compatible with a seizure. Patients were instructed to visit the clinic or report by telephone if any event compatible with a seizure occurred. Follow-up visits were planned 30, 60, and 90 days after the end of treatment and every 3 months thereafter until 30 months after treatment. At the end of the follow-up period, patients still having seizures were referred to the routine care of the hospital’s seizure clinic.

Repeated MRI examination was scheduled to take place 6 months after treatment and CT examinations to take place 12 and 24 months after treatment. Follow-up scans were read by a neuroradiologist who was unaware of the patients’ treatment assignments and who was instructed to report any increase in the number of lesions, any increase in the size of a lesion (by more than 1 cm in diameter), or the development of hydrocephalus.

A data safety and monitoring board composed of two neurologists and one biostatistician met every six months to examine all adverse events and review the progress of the study. Two of the authors analyzed the data.

**STATISTICAL ANALYSIS**

The sample size of 120 patients was chosen to provide the study with 90 percent power to distinguish between a 30-month cumulative incidence of seizure of 70 percent in the placebo group and 35 percent in the albendazole group, with a 5 percent two-sided type I error and 20 percent loss to follow-up. At the initial meeting of the data safety and monitoring board, before any patients were enrolled, it was decided that the primary outcome would be the number of seizures with generalization (including generalized seizures, complex partial seizures and partial seizures with secondary generalization), because of their effect on the life of the patients. Partial seizures were analyzed separately. Seizures were analyzed both with respect to the entire study period and with respect to each of several relevant periods within it: the first month after discharge from the hospital, the first year of follow-up (during antiepileptic-drug therapy), and the first six months after the antiepileptic therapy had begun to be tapered.

The decision to analyze data from the first month separately was made in the early stages of the trial, before any data analysis, because the rate of seizures can increase after corticosteroid tapering.

Since data from patients who remained seizure-free for 6 months after drug tapering were censored from further analysis (as early as 18 months after the start of treatment, resulting in variable follow-up periods), we also analyzed results censored as of 18 months, so that any follow-up bias would be eliminated.

In any given observation period, a Poisson regression model was fitted to the number of seizures of the specified type experienced by each patient, with a dichotomous variable used for the randomly assigned treatment regimen. Within-person correlation was accounted for with the use of a quasilikelihood approach, through the calculation of Pearson’s scale parameter. This population-averaged model, which reproduces the raw rates, was coded before seizure distributions were examined; no other types of regression models were fitted. In adjusted analysis, the Poisson regression models contained variables that remained at a significance level of $P<0.20$ after a backward-selection procedure. The variables, data for which were obtained at baseline, were age, sex, number of viable cysts, prior total number of seizures, prior number of generalized seizures, and prior duration of illness. The latter four variables were rendered dichotomous by comparing the highest quartiles with all the other quartiles. Efficacy was calculated as $100 \times \left(1 - \frac{\text{rate in the albendazole group}}{\text{rate in the placebo group}}\right)$; a negative value indicated that the rate of seizures in the albendazole group was greater than that in the placebo group. In a separate set of Poisson models, we modeled seizure rates as a function of whether a patient was free of active lesions at his or her six-month MRI, but without incorporating any treatment variable. Bivariate analysis was based on the chi-square test, two-tailed Fisher’s ex-
act test, or Mann–Whitney test. An interim analysis for efficacy was performed when there were 28 patients with at least one seizure with generalization; the trigger point at which stopping the trial could be considered was an alpha level of 0.0035. All reported P values are two-sided. Analyses were carried out with the use of SAS software (version 8).

RESULTS

Of 139 patients who underwent MRI to assess their eligibility for the study, 19 were not enrolled, for the following reasons: the presence of only degenerating cysts (1 such cyst in 8 patients and more than 1 in 2), the presence of more than 20 viable cysts (in 6 patients), the existence of other diseases (in 2 patients), and the request for open treatment (in 1 patient). A total of 120 patients were included in the study and were randomly assigned to a study group (60 patients to the albendazole group and 60 patients to the placebo group). The study cohort included 61 male patients and 59 female patients; their mean (±SD) age was 33±13 years (range, 16 to 65). There were no statistically significant differences between the two treatment groups in terms of base-line characteristics (Table 1).

Four patients did not receive the study drugs: two did not return to the hospital for admission, one refused to take an antiepileptic drug, and in one a brain-stem cyst was found on MRI and the attending neurologists decided not to expose her to antiparasitic therapy. Thus, 116 patients (57 assigned to albendazole and 59 to placebo) received the study medication and were the subject of the analyses. All the patients who initiated treatment received the complete 10-day dosage.

Seven patients from each group were lost to follow-up. Two additional patients were excluded from follow-up analysis: one requested albendazole treatment, and the other bought and ingested 400 mg of albendazole to treat intestinal worms.

Twelve patients, six from each group, were readmitted to the hospital because of seizures. Potential causes were identified in nine: poor compliance with their antiepileptic-drug regimen (in five), corticosteroid tapering (in two), hyperemesis of pregnancy (in one), and alcohol ingestion (in one).

SIDE EFFECTS

The proportion of patients who had seizures, headaches, or other neurologic symptoms during treatment was similar in the two study groups (Table 2). Non-neurologic side effects included abdominal pain, nausea, and diarrhea. In one patient, the liver-enzyme levels were higher than normal at the 18-month evaluation, but they became normal after her dose of phenytoin was reduced.

Adverse events occurred in three patients, all in the placebo group. One patient became pregnant and was later readmitted (as noted above) for control of seizures, which were probably related to hyperemesis of pregnancy (nausea, vomiting, and dehydration). One patient returned one day after discharge from the hospital with blurred vision and a left-sided motor deficit, caused by bleeding from a brain-stem arteriovenous malformation (which had been missed in the enrollment evaluation). His condition was stabilized, but right hemiparesis and tremor persisted one year later. One patient was diagnosed as having gastric cancer and died during follow-up.

SEIZURES DURING FOLLOW-UP

During the overall follow-up period (months 2 to 30), patients in the albendazole group had 46 per-
The rate of seizures with generalization was 32 percent (95 percent confidence interval, 19 to 43 percent; \(P=0.01\)) (Table 3). Adjustment for base-line covariates had little effect on seizure occurrence. The efficacy of albendazole tended to be highest between 2 and 12 months after treatment. Its lowest efficacy (14 percent) was observed in patients with the highest number of seizures with generalization (95 percent confidence interval, 20 to 86 percent; \(P=0.01\)) (Table 3). Adjustment for base-line covariates had little effect on these findings. The efficacy of albendazole tended to be highest between 2 and 12 months after treatment. Its lowest efficacy (14 percent) was observed for the treatment of seizures with generalization during the first month after treatment. By the second month, however, this pattern had reversed, and its efficacy exceeded that of placebo (Fig. 2).

When the analysis was restricted to the initial 18 months, the decrease in the rate of partial seizures was 32 percent (95 percent confidence interval, 20 to 86 percent; \(P=0.01\)) (Table 3). Adjustment for base-line covariates had little effect on these findings. The efficacy of albendazole tended to be highest between 2 and 12 months after treatment. Its lowest efficacy (14 percent) was observed for the treatment of seizures with generalization during the first month after treatment. By the second month, however, this pattern had reversed, and its efficacy exceeded that of placebo (Fig. 2).

Other side effects of note included rash, diarrhea, abdominal pain, nausea, headache, dizziness, paresthesia, paresis, and paresis. The rash remitted immediately after phenytoin treatment was suspended. Other side effects were less frequent and less severe. The most common side effect was rash, which occurred in 12 percent of the placebo group and 20 percent of the albendazole group. Diarrhea occurred in 6 percent of the placebo group and 4 percent of the albendazole group. Abdominal pain occurred in 3 percent of the placebo group and 2 percent of the albendazole group. Nausea occurred in 1 percent of the placebo group and 2 percent of the albendazole group. Headache occurred in 1 percent of the placebo group and 2 percent of the albendazole group. Dizziness occurred in 1 percent of the placebo group and 2 percent of the albendazole group. Paresthesia occurred in 1 percent of the placebo group and 2 percent of the albendazole group. Paresis occurred in 1 percent of the placebo group and 2 percent of the albendazole group. A total of 36 patients (64 percent) had at least one active lesion. Among those with enhancing lesions six months after treatment had 62 percent fewer seizures (95 percent confidence interval, 94 to 93 percent; \(P=0.01\)) than those who had at least one active lesion. Among those without active lesions at six months, there was a slightly greater reduction in the number of seizures with generalization than in the number of partial seizures, although the difference was not statistically significant.

Tapering of antiepileptic drug therapy was initiated in 77 patients (41 in the albendazole group and 36 in the placebo group). Partial seizures after dose reduction or withdrawal occurred in five patients (two in the albendazole group and three in the placebo group), and crisis with generalization occurred in eight (two in the albendazole group and six in the placebo group, \(P=0.14\)). Sixty-four patients (36 of 57 in the albendazole group [63 percent] and 28 of 59 in the placebo group [47 percent], \(P=0.13\)) did not have a crisis during the six-month period after antiepileptic-drug tapering had begun.

### Evolution of Cysts

Follow-up MRI was performed at six months in 109 patients (55 in the albendazole group and 54 in the placebo group). Thirty-two of the 57 patients in the albendazole group (56 percent) had no seizures during the follow-up period from month 2 to month 30. Thirty-two of the 59 patients in the placebo group (51 percent) had no seizures during the follow-up period from month 2 to month 30. A total of 64 patients (32 in the albendazole group and 28 in the placebo group) had at least one seizure during the overall trial, including the treatment period and the first month after treatment. The distribution of the number of seizures was similar in the two groups (Table 3). Most of the difference in the number of seizures occurred among patients who had 10 or more seizures; the two patients with the highest numbers of seizures (47 and 144) were both in the placebo group. There were 46 more seizures in the placebo group than in the albendazole group. Patients in the placebo group had a greater tendency to have seizures with generalization (22 of 59 patients, vs. 13 of 57 patients in the albendazole group; risk ratio, 1.63; 95 percent confidence interval, 0.91 to 2.92; \(P=0.13\)). Six patients in the placebo group but none of those in the albendazole group had more than three seizures with generalization (Table 3).

Patients who had no active lesions (cysts or enhancing lesions) six months after treatment had 62 percent fewer seizures (95 percent confidence interval, 94 to 93 percent; \(P=0.01\)) than those who had at least one active lesion. Among those without active lesions at six months, there was a slightly greater reduction in the number of seizures with generalization than in the number of partial seizures, although the difference was not statistically significant.
The use of antiparasitic drugs in neurocysticercosis has been the subject of intense controversy for more than 20 years. The introduction of praziquantel in 1979 was enthusiastically received, but soon afterward, some authors claimed that there was no need to kill a parasite that existed in good symbiosis with the brain. Two retrospective studies published in 1992 found striking differences in the evolution of seizures in favor of antiparasitic treatment, but they were criticized because of their clear, built-in selection bias. By contrast, an open, controlled trial published in 1995 showed no significant differences among patients treated with albendazole, praziquantel, or corticosteroids alone in the evolution of seizures or even in the radiologic evolution of cysts.

In our controlled study, there was a significant reduction in the rate of seizures with generalization and a nonsignificant decrease in the rate of partial seizures during follow-up among the patients who received albendazole as compared with those who received placebo, although most of these benefits
appeared to accrue to a relatively small number of patients. Moreover, cysts in the brain resolved much faster after albendazole therapy than after placebo, as has previously been shown in treatment studies in pigs and in uncontrolled series of patients. This finding refutes the hypothesis that cysts naturally resolve within a short period. An alternative, though highly unlikely, possibility is that the short-term administration of dexamethasone may have altered the immune equilibrium in the treatment group and caused cyst destruction.

More patients in the albendazole group than in the placebo group had seizures during treatment and during the first month of follow-up. This effect results from the acute perilesional inflammation that follows exposure to parasite antigens as a result of the drug’s attack on the cyst and is potentially preventable with the use of higher doses of corticosteroids. The trend reversed itself after month 2, however, and there was a persistent decrease in the number of seizures in the albendazole group as compared with the placebo group. The effect was not complete, however, and there was always a background level of seizures in the treatment group. Since not all cysts are destroyed by a course of albendazole, seizures associated with residual lesions could have diluted the treatment effect seen in the main analysis according to treatment group.

A major factor in the confusion surrounding antiparasitic treatment in neurocysticercosis is the variety of parasite stages that may be involved. Stage definition is crucial for prognosis and management, and we restricted our conclusions to patients with viable parenchymal cysts, who constitute the majority of patients with neurocysticercosis in Latin America. In contrast to other series, we included patients who had live cysts with initial signs of inflammation (perilesional contrast enhancement and edema on imaging studies), provided that the cysts had a visible liquid content. The reason for this is that patients who have only viable, noninflamed cysts are a minority, and we wanted the results of our study to apply to the day-to-day clinical management of patients with neurocysticercosis. Not all viable cysts with signs of inflammation disappear over the short term. In fact, only about half of such cysts resolved over a six-month period in the placebo group. Subgroup analysis confirmed a significant effect of antiparasitic therapy on the radiologic evolution of cysts with inflammation.

Whereas parenchymal neurocysticercosis progresses only rarely (and, when it does, progresses slowly), most extraparenchymal forms of neurocysticercosis are associated with disease progression and hydrocephalus. The lesions in subarachnoid cysticercosis may grow to a diameter of several centimeters and cause intracranial hypertension. Subarachnoid cysticercosis of the sylvian fissure mimics parenchymal cysticercosis. Not to un-
undertake antiparasitic therapy in such cases could allow disease progression and even risk the patient’s life. An additional, and commonly neglected, point of discussion is that most patients feel highly uncomfortable leaving a parasite living in their brain.

The presence of calcifications in the brain is a known risk factor for seizure relapse. A higher proportion of cysts calcified in the treatment group than in the placebo group, but there were fewer patients with seizures in the treatment group. Whether this difference in calcification reflects faster resolution of the lesion and shortening of the natural evolution process with albendazole treatment or whether there is a true difference in the proportion of residual calcifications after parasite death will be evident in the long-term follow-up of our patients.

Because of globalization, many clinicians in industrialized countries who are unfamiliar with neurocysticercosis are now faced with this disease. They should be aware that there are cases in which antiparasitic therapy is not indicated, because the risks of severe side effects may outweigh the potential benefits. However, these cases are infrequent and involve mainly patients who have massive brain infections. In our study (which included only patients with 20 or fewer parenchymal cysts), the side effects of active treatment were mild and included abdominal pain and nausea, which were probably due to the dexamethasone.

In summary, none of the major arguments against the use of antiparasitic therapy were supported by our data. An argument against antiparasitic therapy could still be made, given the costs associated with the treatment and hospital admission and the small risk of cyst growth without it. There is also the hypothetical risk that albendazole could leave more residual calcifications than would otherwise be present, although such calcifications were not associated with increased seizure activity in our study. Yet the benefits of albendazole therapy in decreasing the numbers of seizures outweigh these arguments, and we recommend the use of antiparasitic treatment as part of routine practice in the management of parenchymal brain cysticercosis.

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APPENDIX

The other members of the Cysticercosis Working Group in Peru who collaborated in this study include S. Rodriguez (Instituto de Ciencias Neurologicas, Lima, Peru), M. Tovar and M. Verastegui (Universidad Cayetano Heredia, Lima, Peru), and V.C.W. Tsang (Centers for Disease Control and Prevention, Atlanta).

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