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Short course of albendazole therapy for neurocysticercosis: A prospective randomized trial comparing three days, eight days and the control group without albendazole

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ABSTRACT: Anthelmintic therapy with albendazole for parenchymal cerebral cysticercosis, despite its widespread acceptance, is still the subject of controversy. In this prospective, randomized clinical trial, we compared the effectiveness of two regimens of albendazole therapy for neurocysticercosis against each other and against symptomatic therapy alone. A first group (27 patients) received albendazole for 3 days, a second group (27 patients) received albendazole for 8 days, and a third group (29 patients) received only symptomatic treatment. Effectiveness of albendazole was 85.8% with no difference between the 3 and 8-day groups of treatment. Improvement of the patients in the control group was 34.4%. Complete resolution of cysts was obtained in 77.7% of the patients who received albendazole. Two years after therapy, there was no difference in the number of patients free of seizures, when comparing the three groups of treatment. The ultra-short course of treatment with albendazole for 3 days was effective in our patients. Therapy with albendazole for 8 days did not provide additional benefits.

RESUMEN: Existe controversia en la efectividad del tratamiento antihelmíntico para la cisticercosis, a pesar de su amplia utilización. En este estudio prospectivo y randomizado, comparamos la eficacia de dos regímenes de albendazol contra un tratamiento sintomático. Un grupo de 27 pacientes recibió albendazol por 3 días, un segundo grupo (27 pacientes) recibió albendazol por 8 días y un grupo control (29 pacientes) no recibió tratamiento específico. El porcentaje de reducción de quistes en los dos grupos de pacientes que recibieron albendazol fue del 85.8%, sin diferencia significativa entre ambos grupos. Por el contrario, solo el 34.4% de los quistes que no recibieron tratamiento desaparecieron. Una resolución completa de los quistes se observó en el 77,7% de los pacientes tratados con albendazol. Dos años luego del tratamiento, no hubo diferencia en el número de pacientes libre de crisis convulsivas en los tres grupos de tratamiento. Concluimos que el curso de 3 días con albendazol es eficaz para la destrucción de cisticercos en el parénquima cerebral. Aumentar el curso de tratamiento a 8 días no aumenta la eficacia del albendazol.

The first successful medical treatment for human neurocysticercosis (NCC) was the administration of praziquantel [1,2]. Albendazole appeared shortly thereafter as a sound therapeutic alternative to praziquantel [3,4]. Albendazole is considered the drug of choice for treatment of NCC [5], owing to its greater effectiveness, higher tolerance, shorter time of treatment, and lower cost compared to praziquantel [5-8]. The length of NCC treatment with antiparasitic drugs has declined gradually, from 30 to 3 days [1-5]. A single-day praziquantel therapy has been proposed as a regimen that exerts cysticidal effects similar to those produced by longer courses of praziquantel [9]. Since evidence of the results of effectiveness and duration of the NCC treatment with albendazole has been inconclusive [10-13], we conducted a randomized clinical trial of albendazole treatment for three and eight days, and compared their effectiveness with a control group that did not receive antiparasitic treatment.

Patients and Methods

Between January 1989 and December 1996, we identified and included all patients who came to the Department of Neurology of Eugenio Espejo Hospital, Quito-Ecuador, with a new diagnosis of NCC on the basis of characteristic CT findings. The designation of the patient to a treatment group was made randomly, and allocated to one of the groups on a sequential basis according to the admission number. All patients signed an informed consent prior to being enrolled in the trial. Once treatment was allocated, a neurologist administered the corresponding therapy, whereas a neurologist blinded to treatment allocation conducted the follow-up. We included 95 patients in a prospective, randomized clinical trial. Follow-up continued until December 1998. The study design had been previously approved by the Ethics Committee of the Eugenio Espejo Hospital.

Inclusion Criteria: Men and women of all ages, with neurological signs and symptoms for between one week and 3 years before admission to our study, with CT showing one to six nonenhancing parenchymal brain cysts without perilesional edema, with or without calcifications. A positive CSF ELISA was not required for inclusion.

Exclusion Criteria: We excluded patients whose CT showed ringlike or nodular enhanced cysts and/or edema surrounding the lesions, as well as those with subarachnoid or intraventricular cysts or hydrocephalus. In addition, patients who had previously been treated with either albendazole or praziquantel, pregnant women, and those with clinical evidence of intracranial hypertension were excluded.

Evaluation: All the patients had an initial assessment that included a neurological examination, plain and contrast-enhanced CT of the brain, CSF analyses including cell count, glucose, total proteins and ELISA for detection of anticysticercal antibodies, and a metabolic workup including hematologic, biochemical and routine liver function tests. At the beginning of the study, all patient had good general health. We explained patients that they could not take albendazole or any other antiparasitic drug during the study. All the relatives living with the patients were treated for tapeworm infection.

Treatment Groups: All patients were hospitalized for an initial evaluation. During hospitalization they received symptomatic treatment for headache and epilepsy, until they were asymptomatic and neurologically stable. Patients who were randomized for treatment with albendazole for 3 or 8 days remained in the hospital until 3 days after completing the treatment. Patients who did not receive antiparasitic medication remained until all the complementary tests were performed and they were asymptomatic.

After informing the patients about the study and once they agreed to participate, we allocated each patient to one of the following groups: Group 1, receiving 15 mg of albendazole per kilogram of body weight for 3 days; Group 2, receiving 15 mg of albendazole per kilogram of body weight for 8 days; and Group 3, who did not receive albendazole. In addition, all patients with seizures received anticonvulsive drugs, including carbamazepine and phenytoin, administered as monotherapy. None of the 95 patients received steroids.

Clinical examination was performed every day during treatment and every month afterwards up to 3 months and afterwards at 3-month intervals for at least 2 years. CSF examinations were performed on the day before the start of treatment and one day after the end of the trial.

Follow-up: The evolution of parenchymal brain cyst was monitored by repeated CT scans. Mean and total numbers of cysts were counted during the initial examination, at 3 months, and 12 months after treatment. Patients were divided into two groups according to the number of cysts: those with a single cyst, and those with 2 to 6 cysts. Evaluation of the number of cysts on CT at baseline and at follow-up was performed by a single neuroradiologist (GD) blinded to treatment allocation. Similar axial sections were taken in initial and control CTs to assess the same cysts in subsequent follow-ups. In the patients whose seizures recurred after the end of the study, brain CT-scan was repeated to verify if a new infection had occurred.

Assessment of Treatment: We determined the number of cysts as our primary outcome variable, and the number of patients who were free of seizures as our secondary outcome variable. We established two independent indicators for a successful therapeutic response: a) complete response with disappearance of all the cysts on CT, and b) reduction or absence of seizures in the patients, with a follow-up of more than two years.

Statistical Analysis: We performed the chi-square test and ANOVA for demographic comparisons and the chi-square test for the number of cysts before and after treatment. We used the chi-square test and nonparametric Wilcoxon signed-rank test to analyze the independent indicators of a therapeutic response among the groups of treatment. In addition, we used ANOVA to compare the cells and proteins of the CSF in the 3 groups of the study.

RESULTS

Over a period of 8 years, 95 patients with NCC met the criteria to become part of the study. Six patients, two in each group, were excluded because they could not guarantee good compliance and two patients because they had a concomitant stroke; one of these patients was allocated to the group that would receive albendazole for 3 days and the other to the group receiving albendazole for 8 days. Eighty-seven patients started treatment after the randomization. Four patients dropped out of the study,

because we were unable to obtain complete information from them for at least 2 years after therapy was started. One patient belonged to the 3-day albendazole group, two to the 8-day albendazole, and the other to the control group. The results of the remaining 83 patients are presented (Table 1). ELISA test in CSF was positive in 60 patients (72%). No differences were found when the treatment groups were compared with respect to age, sex, the total number of cysts, number of single cysts and of two to six cysts, and the number of patients with seizures. The average age of the 83 patients was 33.4 ± 15.2 years (age range, 12 to 80 years). The mean duration of follow-up during the trial was 31.4 months. We found 147 viable cysts in the 83 patients (Table 2). The average number of cysts in the 54 patients who received albendazole was 1.8 whereas the average number of cysts of the 29 patients who did not receive the drug was 1.9.

At the first follow-up evaluation, 3 months after antiparasitic treatment (Table 2), 30 (36.1%) of the 83 patients were without cysts ($p < 0.001$). At the second follow-up evaluation, 52 (62.6%) of the patients were without cysts ($p < 0.05$). Thirteen (61.9%) of the 21 patients with single cysts who received albendazole were without cysts in the first evaluation and 17 (80.9%) in the second evaluation. Two patients (20%) of the control group with single cysts were without cyst in the first evaluation and five (50%) in the second. Fifteen (45.4%) of the 33 patients with multiple cysts who received albendazole were without cysts in the first follow-up evaluation and 25 patients (75.7%) in the second evaluation. Three (15.7%) of the 19 patients of the control group with multiple cysts were without cysts in the first evaluation and 5 (26.3%) in the second. Twenty-eight of the 54 patients (51.8%) who received albendazole were without any cyst at the first follow-up and 42 (77.7%) at the second. Two of the 29 patients (6.8%) of the control group were without any cysts at the first assessment and 10 (34.4%) at the second.

In the two evaluations, when comparing the patients with single cysts, who received albendazole for 3 and 8 days, we did not find a statistical difference in the number of patients who were without cysts (Table 2). When comparing each one and the two groups of treatment who received albendazole with the control group, we found significant differences in the number of patients with single cysts who were without cysts, in both the first ($p < 0.001$) and the second evaluations ($p < 0.05$). In the patients with multiple cysts who received albendazole for 3 and 8 days, we did not find differences in the number of patients who were without cysts, in the first and second evaluations. There was a significant difference when comparing the two groups of treatment who received albendazole and the control group, in both the first ($p < 0.001$) and the second ($p < 0.05$) evaluations (Table 2). When comparing the total number of cysts in the three study groups, there was no difference between the two groups that received albendazole, but there was a significant difference when comparing the two groups that received antiparasite treatment with the control group, in both the first ($p < 0.001$) and the second evaluations ($p < 0.05$).

Fifty-eight (69.8%) of the patients included in the study had seizures. Eighteen patients (21.6%) had more than one seizure per month (Table 3). All the patients with seizures received anticonvulsive treatment for more than 2 years. Twenty-seven patients (46.5%) with epilepsy were without seizures two years after the antiparasitic treatment (Table 3). We did not find significant differences in the number and percentage of the patients who were free of seizures for at least 2 years when comparing the three groups of the study.

During the antiparasitic treatment, 8 patients (29.6%) of the group with albendazole for 3 days, and 6 patients (22.2%) of the group with albendazole for 8 days suffered headaches. Seizures were recorded in one patient from the group with albendazole for 3 days, and in one patient from the group with albendazole for 8 days. Two patients displayed focal motor deficit during treatment, one in the group that received albendazole for 3 days and one in the group that received albendazole for 8 days. There was vomiting and dizziness among 14 patients who received albendazole. These symptoms appeared between the second and third day of treatment, both in patients who received 3 days and in those who received 8 days of albendazole. In these two groups, the rise in cells and proteins was similar in the CSF analysis one day after treatment (Table 4). CSF in the control group did not show significant modifications during the study. During the follow-up, one patient from the group with albendazole for 8 days required a ventricular shunt due to obstructive hydrocephalus.

DISCUSSION

Praziquantel and albendazole are effective drugs for the treatment of cysticercosis of the brain parenchyma [7,14,15]. Currently, albendazole is considered the drug of choice for treatment of NCC [5]. Owing to the terms used to select the patients and the selection and measurement of outcome variables that were used in the studies conducted with these anti-parasitic drugs [5,7,14-16], their results have been considered inconclusive [11,12].

Albendazole was initially administered at daily doses of 15 mg/kg/day for 30 days; nevertheless, further studies showed that, at similar doses, the length of therapy could be shortened, from 30 days to 8, 7 and 3 days without lessening the efficacy of the drug [4,7,8,15,-17]. Most of these studies were open-ended, with a short duration of follow-up and similar effectiveness. Owing to the need to reduce the dose and the cost of the therapy, ultra-short treatments involving a single-day administration of praziquantel for NCC have been applied and they have proven to be effective [9].

When we compared the results of the first follow-up CT (3 months after treatment) with a baseline CT, we found that a high number of the patients who received albendazole for 3 and 8 days, were without cysts, and there was a significant difference with the control group. When comparing the number of patients with total disappearance of cysts, we did not find any difference between the two groups that received albendazole, but there was a significant difference when comparing them with the control group. This difference was maintained in the second follow-up CT. When comparing the first and second follow-up (3 and 15 months after treatment), between the two groups that received albendazole we found no statistical difference in the number of patients that were without cysts. These findings suggest that albendazole produces the death and disappearance of parenchymal brain cysticercus, and confirms our previous findings that the ultra-short treatment of 3 days with albendazole is as effective as the 8-day treatment [17].

In most studies on drug therapy for NCC, clinical variables were not well defined. Of the many signs and symptoms of NCC, epilepsy is the most frequent and the most easily identified and quantified. Improvement in seizure control has been used as an outcome variable to evaluate the effectiveness of antiparasitic drugs [18,19]. In those studies, seizures have persisted in the control group that was untreated with antiparasitic drugs, even though a concurrent control group selected in a manner similar to those treated was not identified (1-4,7,8,15-19). Our study, in concordance with a previous study [13], showed that the control of the seizures in these patients is not modified by albendazole therapy. These results, along with the lack of sufficient evidence in pathological studies, suggest that antiparasitic drugs do not produce a more profound cerebral cicatrix than symptomatic therapy [20].

Our study showed a statistically significant difference in the radiological prognosis, when comparing the groups treated with albendazole with the control group, in the number of patients without cysts, or with decline in the number of cysts by group of treatment, and in the mean reduction in cysts per patient. We did not find differences in the radiological prognosis when comparing the previously indicated parameters between the patients who received albendazole for 3 and 8 days. Our study did not show any statistical difference in the clinical prognosis; the number of patients who were free of seizures, in the three groups, was similar.

The evidence of medical treatment of NCC has been persuasive but inconclusive [10], and this has led some authors to doubt its effectiveness [11-13]. Some revisions have been critical with the trials of NCC, especially the way of selecting the patients and the selection and measurement of outcome variables. Our study is a controlled randomized trial conducted during 8 years and based on our previous study of a short treatment for 3 days [17], which demonstrated an effectiveness similar to the more prolonged treatments. None of our patients received corticosteroids along with albendazole, and therefore their results were not affected by interactions with this drug [13].

The results of our controlled trial, with a follow-up of more than 2 years, show that the ultra-short course of treatment with albendazole for 3 days for parenchymal brain cysts is similar to, and is not significantly different from, the 8-day course of treatment. In addition, our study shows that, when comparing the groups treated with albendazole with the control group, the rate of disappearance of cystic lesions, and the number of patients without cysts were significantly higher after albendazole therapy. Our study also shows that the control of seizures is not modified by albendazole.

In conclusion, although the size of the sampling of our study is small, it suggests that the 3-day course of albendazole therapy is safe, effective, and has the obvious advantage of better patient compliance and reduced costs of therapy. New controlled studies, with larger numbers of patients are needed to accumulate further evidence that short courses of albendazole are effective.

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Table 1. Demographic, imaging, and clinical characteristics of 83 patients with NCC.

	Albendazole 3-day group (n = 27)	Albendazole 8-day group (n = 27)	Control group (n = 29)
Age years (mean \pm SD)	33.6 \pm 15.6	33.9 \pm 16.1	32.9 \pm 14.1
Sex (man/woman)	12/15	12/15	12/17
Average follow-up during trial (months)	33.1 \pm 11.9	31.1 \pm 6.4	30.2 \pm 10.8
Total cysts (mean)	49 (1.8)	43 (1.7)	55 (1.9)
Single cyst	9	12	10
Two to six cysts	40	31	45
Total patients with seizures	18	20	20

Nonsignificant difference (chi-square test)

Nonsignificant difference (ANOVA)

Table 2. Number of patients, number of cysts and mean at baseline and follow-up at 3 and 12 months after treatment

Evaluations	Albendazole 3-Day Group		Albendazole 8-Day Group		Control Group	
	No. patients	No. cysts Total (mean \pm SD)	No. patients	No. cysts Total (mean \pm SD)	No. patients	No. cysts Total (mean \pm SD)
At baseline CT scan						
Total	27	49 (1.8 \pm 0.7)	27	43 (1.7 \pm 0.7)	29	55 (1.9 \pm 0.7)
Single cyst	9	9	12	12	10	10
Multiple cysts	18	40	15	31	19	45
First follow-up (3 months)						
Total	27	18 (0.6 \pm 0.7)	27	13 (0.4 \pm 0.5)	29	47* (1.6 \pm 0.8)
Single cyst	10	10	11	11	11*	11
Multiple cysts	4	8	1	2	16*	36
Without cysts	13	-	15	-	2*	-
Second follow-up (12 months)						
Total	27	7 (0.2 \pm 0.5)	27	6 (0.2 \pm 0.4)	29	28* (0.9 \pm 0.8)
Single cyst	5	5	6	6	12*	12
Multiple cysts	1	2	-	-	7*	16
Without cysts	21	-	21	-	10*	-

Statistically significant when comparing the number of patients with cysts and the number of cysts of the groups that received albendazole with the control group in the first evaluation ($p < 0.001$) and the second evaluation ($p < 0.05$) after treatment (chi-square test and Wilcoxon test).

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