CLINICAL EVALUATION OF ALBENDAZOLE AND PRAZIQUANTEL IN THE TREATMENT OF CEREBRAL CYSTICERCOSIS

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Abstract. One hundred consecutive patients presenting with symptoms and signs of neurocysticercosis, confirmed by neuroimaging techniques were randomly assigned to treatment with either praziquantel 50 mg/kg/day for 15 days or albendazole 15 mg/kg/day for 30 days. All patients were treated also with steroids for 42 days. Follow-up was for 90 days for response to treatment and for at least 1 year for recurrence. Although similar numbers of patients showed no improvement in neuroimaging criteria at 3 months, the response to albendazole was more pronounced with larger numbers showing marked improvement or disappearance of lesions. Similar findings were apparent, with resolution of the presenting neurological signs and symptoms being more frequent, in the albendazole group. Electroencephalographic changes were also normalized. The use of steroids eliminated the frequently observed headache that has been seen during the first few days of treatment and permitted severe cases to be treated. Both albendazole and praziquantel appear to be effective at the doses used, with albendazole showing a slightly better overall response.

INTRODUCTION

Cysticercosis has been reported wherever pigs are extensively reared under unhygienic conditions, particularly where man and pig live in close proximity. Almost every organ in the human body has been found to be infected by cysticeri, but subcutaneous tissues, muscles, eyes and brain are most commonly affected. The larval parasite seems to have a special predilection for the central nervous system, where it can invade the parenchyma, the subarachnoid spaces, and the ventricular system. The initial stages of infection may go unnoticed, the cerebral manifestations usually being the cause of medical consultation, due to the appearance of significant clinical symptoms. These depend on the parasite's developmental phase, the number and localization of the cysts, and may mimic a number of neurological conditions.

Recent studies (Sotelo *et al,* 1988) have demonstrated the efficacy of both praziquantel and albendazole for the clinical treatment of cystic parenchymatous cerebral cysticercosis. This has, however, been based more on tomographic rather than clinical end points. Here we present a series of 100 consecutive cases of neurocysticercosis, 50 treated with praziquantel and 50 with albendazole. Therapeutic efficacy was comprehensively evaluated on the basis of clinical, neurophysiological, and tomographical criteria.

MATERIALS AND METHODS

One hundred consecutive patients suffering from cerebral cysticercosis attending the outpatient clinic of the Center for Research and Training in Neurosciences in Quito, Ecuador, were included in this study. The first 50 were treated with praziquantel (50mg/kg/day for 15 days) and the second fifty with albendazole (15mg/kg/day for 30 days). The diagnosis was based on the presence of at least three of the following criteria: a) epidemiological history (Cruz *et al,* 1989),b) neurological signs and/or symptoms, c) neurophysiological changes, and d) neuroimaging criteria (computed tomography [CT] or nuclear magnetic resonance [NMR] evidence).

Patients suffering from any development phase of the parasite in one or more of the usual locali-

zations (parenchymatous, subarachnoid or ventricular) were included.

Patients were classified as embryonal (Ramos *et al,* 1986), encephalitic (Mitchell and Crawford 1988), cystic (Sotello *et al,* 1988), calcific (Escobedo *et al,* 1987) or mixed forms, and were subsequently analysed according to this classification.

The disease was considered active in the presence of acute or chronic neurological symptoms with clear neurophysiologic abnormalities and with positive immunological testing, or neuroimaging criteria.

All patients received a complete clinical and neurological evaluation prior to, during the first 72 hours, and at 8, 15, 30, 60 and 90 days after treatment. Follow-up examinations were performed every three months thereafter for recurrence. All patients had plain and contrast CT scans before and at three months after treatment.

Neurophysiological testing was completed in 48 patients who received praziquantel and in 25 receiving albendazole. Immunological testing and NMR imaging was only performed in those cases who had normal plain and contrast CT and who were suspected of suffering from cysticercosis on clinical and epidemiological grounds.

Both patient groups were hospitalized for the initial 72 hours after beginning specific chemotherapy, and then followed as outpatients. All patients were treated concomitantly with corticosteroids, using the therapeutic scheme proposed by Dowling *et al* (1980). Each patient received 750 mg IV methylprednisolone over the first three days, and oral prednisone in decreasing doses on alternate days until day 45. Anticonvulsants were continued with analgesic and other symptomatic medication prescribed as necessary.

Clinical evaluation was undertaken at 3 months after starting therapy. Patients were classified as no change, slight improvement, marked improvement (asymptomatic but requiring continued medication) or cured.

RESULTS

There were 25 males and 25 females (mean age 38 years) treated with praziquantel and 20 males and 30 females (mean age 36 years).

In the praziquantel group, 8 patients were diagnosed as embryonal stage, and of these, 6 showed slight or marked improvement after treatment. In the albendazole group there was only one patient in this category, and there was no change post-treatment.

CT studies at the three month follow-up demonstrated a complete resolution of all encephalitic lesions in 3 of 4 cases treated with praziquantel and in all 13 patients who received albendazole.

Cystic lesions disappeared in 19 out of 24 patients (79%) treated with praziquantel and in 8 of 10 patients (80%) treated with albendazole. These results were achieved following a single course of treatment. In those patients in whom cystic lesions were apparently unresponsive (5 praziquantel and 2 albendazole) a further course of treatment was given to produce a response. This was successful in both albendazole patients and 3 praziquantel patients, the remaining two requiring a further course of praziquantel before response was seen. One albendazone treated patient with very extensive cystic disease received a higher dose (21 mg/kg/day) continuously for 3 months with resolution of the CT findings.

Thirty-six patients in the praziquantel group had calcified lesions, but only 19 (53%) demonstrated marked improvement or were cured; after albendazole treatment similar improvement occurred in 33/40 (83%). In one albendazole treated patient who had only calcified lesions, reactivation of his presenting symptoms (seizure disorder) occurred 3 months after starting treatment. New encephalitic lesions were apparent on CT and these responded to a second course of albendazole with relief of symptoms.

The extent of disease as well as the intensity of the clinical symptomatology on presentation were comparable in the two groups.

Table 1 shows the clinical neurological picture and its evolution. The most frequent primary symptomatology was a seizure disorder, either generalized or focal, with or without secondary generalization. There was a favorable outcome, ie, marked improvement/cure in 71% of the cases with praziquantel and in 88% with albendazole. Thirty-six percent of the praziquantel and 69% of the albendazole treated patients with intractable headache were markedly improved or cured.

Table 1

Presenting neurological signs and symptoms : outcome at 3 months after treatment with praziquantel (P) and albendazole (A).

Neurological sign/symptom	Pre-treatment		Outcome							
					Improvement					
			No change		Slight		Marked		Cured	
	P	A	P	A	P	A	P	A	P	A
Headache	11	16	3	4	4	1	3	10	1	1
Convulsions	31	25	3	1	6	2	18	12	4	10
Increased intracranial pressure	8	6	2	0	1	0	3	5	2	1
Brainstem signs	-	2	0	0	0	0	0	2	0	0
Miscellaneous	-	1	0	0	0	0	0	1	0	0
Total	50	50	8	5	11	3	24	30	7	12

Table 2

Localization of cysts and outcome at 3 months after treatment with praziquantel (P) or albendazole (A).

Localization	Pre-treatment		Outcome							
					Improvement					
			No change		Slight		Marked		Cured	
	P	A	P	A	P	A	P	A	P	A
Pa	37	42	6	5	8	3	19	24	4	10
Ar	1	2	0	0	1	0	0	2	0	0
Ve	0	0	0	0	0	0	0	0	0	0
Mixed:										
Pa + Ar	11	6	2	0	1	0	5	4	3	2
Pa + Ve	1	0	0	0	1	0	0	0	0	0
Total	50	50	8	5	11	3	24	30	7	12

Pa = Parenchymatous
Ar = Arachnoidal
Ve = Ventricular

Table 2 shows the CNS localization and outcome. Most cases were classified as having parenchymatous disease present: 63% (31/49) praziquantel and 83% (40/48) albendazole treated patients were markedly improved or cured. Where arachnoidal spaces were involved, 66% (8/12) praziquantel and 100% (8/8) albendazole treated patients showed clear clinical improvement.

Electroencephalographic studies revealed

abnormal bioelectric cerebral activity in all cases. Abnormalities found were clearly identified sharp wave foci and paroxysmal bisynchronous epileptic discharges in those cases presenting acute seizure disorders, and non-specific diffuse slow wave changes in patients with other neurological pictures. Most of these abnormalities disappeared after treatment.

Overall, this study shows that with praziquantel there was an improvement in 62% of the cases, as compared to 84% of those treated with albendazole. This difference was statistically significant ($p < 0.05$).

Significant adverse events were not observed during treatment with either drug. Importantly severe headache was not encountered during the early stages, probably due to the use of concommitant high does steroids and all but one patient were managed as outpatients after the first 3 days.

DISCUSSION

The development of new agents to treat cerebral cysticercosis is important for countries where this disease still constitutes a serious public health problem.

Both praziquantel (Cruz, 1983; Spina-Franca *et al,* 1982) and albendazole (Escobedo *et al,* 1987) have recently been shown to be effective in the treatment of cerebral cysticercosis. The present study compared praziquantel and albendazole using clinical and neuroimaging criteria at 3 months as evidence of efficacy in the treatment of this serious condition.

While clinical presentation may vary with the developmental phase, number and localization of the parasites in the CNS, and the immunological status of the host, the natural history of this parasitosis is not completely understood. Periodic follow-ups using clinical examination together with neurophysiological tests, computed tomography and/or magnetic resonance, are necessary to evaluate the efficacy of a proposed treatment.

Although the majority of patients showed response three months after a single course of treatment, not all patients responded equally and treatment regimens, therefore, need to be tailored to the individual case. This was demonstrated in this study where repeat courses or prolonged treatments were necessary in cystic lesions to produce resolution. Longer term follow-up is required to demonstrate the potential for recurrence, either through differential maturation of existing parasites or re-infestation.

Further studies are required to determine the optimum dose and duration of treatment for both drugs. Recently dosage schemes with a duration of 14 or even 8 days have been proposed for albendazole (Sotelo *et al,* 1990).

The use of concomitant steroids may be controversial, but have a number of beneficial effects for patients affected with cerebral cysticercosis. Steroids combat the parasitic vasculitis demonstrated in this type of lesion (Barinagarrementeria and Delbruto, 1989; McCormick *et al,* 1983) and also block the inflammatory reactions caused primarily by parasite death (Sotelo *et al,* 1985a), or secondarily, as a response to the specific chemotherapy (Sotelo *et al,* 1988). This approach may, therefore, permit treatment of patients with raised intracerebral pressure or other complications, and reduce the frequency of headache reported in the early phase of treatment.

It is interesting to note that after treatment with albendazole, in some cases new calcifications appeared where there had been no previous evidence of parasitic lesions by computed tomography. In cerebral cysticercosis, embryonal phases may not be demonstrable by CT scanning, but are positive on magnetic resonance imaging (Sotelo *et al,* 1985b). If the suspect patient has abnormal neurophysiological tests, as seen in all patients in this study, the possibility of cryptic lesions must be considered and NMR performed.

Finally, preventive measures are urgently needed in the short term for those populations living in geographic foci considered hyperendemic for taeniasis/cysticercosis. Chemotherapy targeted on the human carrier has been proposed (Richards and Schantz, 1985) and community-based programs have been carried out successfully using praziquantel (Cruz *et al,* 1989). Improvements in health education and in pig husbandry will also be required before the need for treatment of human cysticercosis becomes unnecessary.

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