TREATMENT OF EOSINOPHILIC MENINGITIS WITH A COMBINATION OF ALBENDAZOLE AND CORTICOSTEROID

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Abstract. To study the efficacy of the combination of albendazole and prednisolone for the treatment of eosinophilic meningitis, we conducted a pilot study among Thai patients with eosinophilic meningitis. Patients were given a 2-week course of prednisolone, 60 mg/day and albendazole, 15 mg/kg/day. The primary observation parameter was the number of patients who still had headache after the 2-week course of treatment. Twenty-six patients were enrolled in the study. There were 3 (11.5%) patients who still had headache after the 2-week course of treatment and the median length of time until complete disappearance of headache was 4 days. Serious side effects were not detected. Treatment for 2 weeks with the combination regimen of albendazole and prednisolone is safe and effective for the treatment of eosinophilic meningitis.

INTRODUCTION

The commonest cause of eosinophilic meningitis is *Angiostrongylus cantonensis*. Acute to subacute severe headache with nonfocal neurological findings, with the exception of an occasional involvement of a cranial nerve, are the most common presenting symptoms (Punyagupta *et al*, 1975). There is no specific treatment. Symptomatic treatment is indicated for symptoms such as headache, nausea, and vomiting. Repeat lumbar punctures are performed in patients with raised intracranial pressure. Recently, a 2-week course of prednisolone was shown to be beneficial in relieving headache (Chotmongkol *et al*, 2000). A trial of specific therapy is still inconclusive. Thiabendazole, mebendazole, and albendazole have some effect in animal infections (Cuckler *et al*, 1965; Maki and Yanagisawa, 1986; Hwang and Chen, 1988). Thiabendazole was ineffective in human angiostrongyliasis (Kliks *et al*, 1982). Albendazole (Hwang and Chen, 1991), or the combination of mebendazole and dexamethasone (Tsai *et al*, 2001) have been used clinically with good results, but details of the trials were not demonstrated. To our knowledge, this is the first report of the outcome of the treatment of eosinophilic meningitis with the combination of albendazole and prednisolone.

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MATERIALS AND METHODS

Study population

Adult patients (aged ≥15 years) who had eosinophilic meningitis and who came to the Out-Patient Department, Srinagarind Hospital and Muncha Khiri Hospital (Khon Kaen, Thailand) were studied. The diagnosis of eosinophilic meningitis was based on findings of ≥10% eosinophils in the CSF, with negative results for Gram, acid-fast bacilli, and India ink staining, cryptococcal antigen testing, and culture.

Patients were excluded if they had undergone a previous lumbar puncture or if they had pregnancy or lactation, or concomitant conditions, such as serious infection.

The severity of headache was classified by using a visual analogue scale: 0 denoted no pain; 1-3, mild pain; 4-7, moderate pain; and 8-10, severe pain (with 10 denoting the worst pain imaginable). A CSF opening pressure of ≥ 300 mm H_2O after the patient was fully relaxed was defined as high CSF pressure.

Treatment

Patients were given prednisolone, 60 mg/day orally in 3 divided doses and albendazole 15 mg/kg/day orally in 2 divided doses after meals for 2 weeks.

Studies to monitor efficacy and toxicity

Before treatment, the following studies were performed: complete blood count; measurements

of blood glucose, electrolytes, serum blood urea nitrogen, and creatinine; and liver function tests. CSF samples were obtained for India ink, Gram, and Ziehl-Neelsen stains, culture for bacteria, determination of opening pressure, total cell counts and differentials, glucose and protein levels, cryptococcal and bacterial antigen tests. Chest radiography was also done.

During treatment, 2 tablets of acetaminophen (500 mg each) were given to relieve headache every 4-6 hours if the headache persisted or recurred. Repeat lumbar puncture was done for patients with severe headache that was not relieved by acetaminophen.

Evaluation

After a baseline evaluation, patients were evaluated at the end of treatment and every 2 weeks until the patients completely recovered. At each visit, a physical examination was done and any adverse events were assessed and recorded. During treatment and until the headache completely disappeared, the frequency of acetaminophen use and repeat lumbar puncture were also recorded. Compliance was checked by the pill-count method.

The day of complete recovery was defined as the first day that the patient thought the headache had disappeared and had taken no acetaminophen nor undergone lumbar puncture, if the headache did not recur within 1 month. For the patients who had post-lumbar headache, the day of complete recovery was defined as the first day that the patient thought the headache had disappeared while the patient was supine and had taken no acetaminophen.

The primary observation parameter in this study was the number of patients who still had headache after the 2-week course of treatment. The secondary parameter was the length of time until the complete disappearance of headache. Information obtained from the subjects and laboratories were recorded on case-record forms. Data was analyzed by descriptive statistics.

RESULTS

Study population

From October 2001 through June 2002, 29 patients were enrolled in the study. Three patients were removed from the study because they were lost to follow-up and the clinical data were incomplete. Therefore, 26 patients were studied. The clinical and laboratory features of the patients were shown in Tables 1 and 2. Before the illness developed, 21 patients had eaten raw pila snails, 1 patient had eaten raw freshwater shrimp, 1 patient had eaten raw liver of the yellow tree monitor, and 3 patients had no history of eating raw food.

Outcome

The number of patients with complete disappearance of headache was 18 at 7 days after treatment, 5 at 8-14 days after treatment and 3 at 15-21 days after treatment. The details of clinical outcomes are shown in Table 3. No gastrointestinal bleeding, hyperglycemia or altered mental

Table 1
Initial clinical features of the study patients.

Feature	N = 26
Age, year, mean (range)	36.5 (15-64)
Sex, male	16
Incubation, day[a]	30 (3-365)
Signs or symptoms	
Headache	
Duration, day[a]	7 (2-60)
Degree	
Moderate	3
Severe	23
Vomiting	12
Stiff neck	11
Fever (T ≥ 38.0ºC)	3
CNP	0

Data are no. of subjects, unless indicated otherwise; CNP=cranial nerve palsy; T=temperature; [a]median (range).

Table 2
Initial laboratory features of the study patients.

Feature	N = 26
Blood eosinophilia (≥700 cells/mm^3)	20
CSF abnormalities	
High opening pressure (≥300 mm H_2O)	7
WBC/mm^3	1,401 (100-5,100)
Eosinophilia, %	53 (18-86)
Protein content, mg/dl	75 (17-207)
Glucose ratio, CSF/blood, %	42 (13-94)

Data are no. of subjects or median (range).

Table 3
Clinical variables of the study patients.

Variable	N = 26
Headache after 14 days of treatment, no. (%) of patients	3 (11.5)
Time until complete disappearance of headache, median day (range)	4 (1-17)
Repeat lumbar puncture, no. (%) of patients	0 (0)
Frequency of acetaminophen use in patients who had complete disappearance of headache within 14 days of treatment, median no. of times	4

status was seen, and there were no cases of recurrent meningitis.

DISCUSSION

In humans, infection by *A. cantonensis* is caused by eating third-stage larvae in raw or inadequately cooked intermediate hosts, such as snails and slugs or transport hosts such as freshwater prawns, frogs, and the yellow tree monitor. When third-stage larvae are ingested, they penetrate the blood vessels of the intestinal tract and are carried to the meninges, where they usually soon die. A presumptive diagnosis may be made for patients who have symptoms of meningitis with CSF eosinophilia and a history of consumption of raw snails. In our patients, although serological testing was not available in our hospital, *A. cantonensis* was most likely the causative agent of eosinophilic meningitis, because most patients had a history of ingestion of raw snails before this illness and had clinical manifestations that were similar to those in the patients described by Punyagupta *et al* (1975).

Although headache is not fatal, it is a distressing symptom that interferes with the personal and professional lives of patients. Supportive treatment, such as analgesic drugs and repeat lumbar puncture are recommended. We recently demonstrated that a 2-week course of prednisolone was beneficial in relieving headache, shortened the median time until resolution of headache, and reduced the need for repeat lumbar puncture (Chotmongkol *et al*, 2000).

The role of antihelmintic agents is still inconclusive. Albendazole was effective in the treatment of *A. cantonensis* in mice. Worm reduction was nearly 100% in mice treated for 14 days (Hwang and Chen, 1988). Theoretically, the neurologic symptoms should be exacerbated as a result of the death larvae, however, albendazole was used clinically without serious side effects (Hwang and Chen, 1991). In our study, we demonstrated good results from the combination of albendazole and prednisolone. In addition, no harmful effects of treatment was demonstrated.

In summary, treatment for 2 weeks with the combination regimen of albendazole and prednisolone is safe and effective for the treatment of eosinophilic meningitis. Further study is necessary to prove the efficacy of this regimen compared to prednisolone alone.

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