INITIAL TREATMENT OF CRYPTOCOCCAL MENINGITIS IN AIDS

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Abstract. The comparison of initial treatment with amphotericin B (0.7 mg/kg/d) plus rifampin (600 mg/d) with amphotericin B (0.7 mg/kg/d) alone for 2 weeks, both followed by fluconazole (400 mg/d) for 8 weeks in the acute treatment of cryptococcal meningitis in AIDS by an open- randomized, controlled, prospective clinical trial is reported. Twenty patients were enrolled in each group. There were no significant differences between the groups in regard to a negative CSF culture for *Cryptococcus neoformans* in the 2nd and 10th weeks of treatment, time until normal body temperature after treatment, number of patients who died, and persistence of high CSF pressure after completion of treatment. Elevated intracranial pressure was an important factor associated with the patients who died. These results indicate that the combination of amphotericin B plus rifampin is not superior to amphotericin B alone.

INTRODUCTION

Cryptococcal meningitis is the most common fungal infection of the CNS in patients with the acquired immunodeficiency syndrome (AIDS). Currently, the initial treatment of choice is amphotericin B (0.7 mg/kg/d), with or without flucytosine, for 2 weeks followed by fluconazole (400 mg/d) for 8 weeks, or until cerebrospinal fluid (CSF) cultures are sterile (van der Horst *et al*, 1997). The results from the treatment regimen of amphotericin B for 2 weeks followed by fluconazole for 8 weeks revealed a clinical response in 83% of patients after two weeks, with negative CSF cultures in 51% and 72% by two and ten weeks of treatment, respectively.

In a recent *in vitro* study, the combination of amphotericin B and rifampin produced a greater effect on the reduction of the minimal inhibitory concentration (MIC) of amphotericin B than when either drug was used individually for *Cryptococcus neoformans* (Srimuang *et al*, 2000). We recently performed a pilot study of an initial treatment with amphotericin B plus rifampin for 2 weeks followed by fluconazole for 8 weeks in 10 AIDS patients with cryptococcal meningitis. At 2 weeks, all had clinically improved and the CSF was sterile in 4 cases. At 10 weeks, all had negative CSF cultures (Chotmongkol and Methawasin, 2000).

We then initiated an open-randomized, controlled, prospective clinical trial to compare the efficacy of amphotericin B plus rifampin with amphotericin B as an initial treatment in the acute therapy of cryptococcal meningitis in AIDS. The results of this clinical trial are reported here.

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PATIENTS AND METHODS

Study population

Adult patients with AIDS (age ≥15 years) who had a first episode of cryptococcal meningitis and who were admitted to the Department of Medicine, Srinagarind Hospital (Khon Kaen, Thailand) and Suppasitthiprasong Hospital (Ubon Ratchathani, Thailand) were studied. A positive test for HIV antibody and a positive CSF culture for *C. neoformans* confirmed HIV infection and cryptococcal meningitis, respectively.

Patients were excluded if they had: altered consciousness; a known allergy to either drug; a white cell count under 1,500/mm^3; a platelet count under 30,000/mm^3; significant impairment of liver function tests (>5 x normal) or renal function (creatinine >3 μg/mm^3); another acute op-

portunistic infection; tuberculosis; were pregnant or lactating. Concomitant therapy with anticoagulants, barbiturates, phenytoin, H_2-blockers or drugs that had potential interactions with triazole and other systemic antifungal therapy was not allowed. The study protocol was reviewed and approved by the institutional review board and the ethics committee of Khon Kaen University.

Sample size and power

In the control group, 70% of the patients were expected to have negative CSF cultures after 10 weeks of treatment, whereas 99% of the patients in the treatment group were expected to have negative CSF cultures. The number of subjects in each group was estimated to be 20, by use of a 2-sided test with an a error of 5% and a β error of 20%.

Randomization and treatment

Subjects gave written informed consent before beginning the study and were randomized to receive treatment. A block-of-4 randomization was used to ensure balance between the groups. In the first two weeks, patients in the treatment group were given amphoterin B (0.7 mg/kg/day) plus rifampin (600 mg/day), whereas patients in the control group were given amphoterin B at the same dosage, only. They all received fluconazole (400 mg/day) for 8 weeks. Prophylactic therapy for *Pneumocystis carinii* was also permitted.

Studies to monitor efficacy and toxicity

Before treatment, the following studies were performed: complete blood count; HIV antibody; measurements of blood glucose, electrolytes, serum blood urea nitrogen; creatinine; hemoculture; and liver function tests. CSF samples were obtained for: India ink preparation; Gram and Ziehl-Neelson stains; bacterial cutlure; determination of opening pressure; total cell counts; differential; glucose and protein levels; and cryptococcal antigen. In addition, chest radiography was done. The cultures for fungi were kept for 30 days before being discarded. All pretreatment studies were repeated at the end of weeks 2 and 10. On each occasion, the CSF pressure was measured after the patients were fully relaxed. Repeat lumbar punctures were done for patients who had a CSF pressure ≥300 mm H_2O.

Evaluation

After baseline evaluation, the patients' conditions were evaluated daily for the first 2 weeks and monthly thereafter until the 10-week study period was completed. At each visit, a physical examination was done and any adverse events were assessed and recorded.

Outcome

Clinical and mycologic outcomes were evaluated. The clinical outcome was considered to be successful if fever, headache, and meningismus were absent. The mycologic outcome was considered to be successful if the CSF culture was negative. In those patients who died, elevated intracranial pressure was considered to be associated with the death if the last known CSF opening pressure was 300 mm H_2O or higher within two weeks of death.

Study design and statistical analysis

The primary outcome of this study was the number of patients in the 2 groups who had negative CSF cultures after 10 weeks of treatment. Information obtained from the subjects and laboratories were recorded on case-record forms. Data were analyzed by descriptive statistics, Student's *t*-test, χ^2 test, and Fischer exact probability test where appropriate.

RESULTS

Study population

From January 2002 through August 2003, 40 patients (20 in each group) were enrolled in our study and completed the course. The clinical presentations were similar in both groups at randomization (Tables 1 and 2). Associated infections were observed in 2 patients in the control group (1 with *Salmonella* bacteremia and 1 with α-hemolytic streptococcal bacteremia).

Outcome

During the treatment period, 1 patient in the study group developed acute blindness, associated with high CSF pressure on the13th day of treatment and 1 patient in the control group developed unilateral 3rd cranial nerve palsy on the 16th day of treatment.

Table 1
Comparison of initial clinical features between patients in the treatment group and the control group.

Feature	Treatment group (n = 20)	Control group (n = 20)
Age, y, mean (range)	30.1±5.1 (23-43)	32.6±6.0 (19-46)
Sex, male	12 (60.0%)	12 (60.0%)
Signs or symptoms		
Headache	20 (100%)	20 (100%)
Duration, d, median (range)	7 (2-21)	7 (2-30)
Fever (T≥ 38.0ºC)	18 (90.0%)	16 (80.0%)
Duration, d, median (range)	7 (2-21)	7 (1-14)
Stiff neck	19 (95.0%)	18 (90.0%)
Papilledema	2 (10.0%)	1 (5.0%)

T = temperature.

Table 2
Comparison of initial laboratory features between patients in the treatment group and the control group.

Feature	Treatment group (n = 20)	Control group (n = 20)
Complete blood count		
Hematocrit, %, mean	32.1±7.0	31.4±6.1
WBC, cells/mm^3, mean	5,479.5±2,407.6	4,897.0±2,307.0
Positive blood culture for *C. neoformans*	9 (45.0%)	0 (0.0%)
CSF abnormalities		
High opening pressure (≥300 mm H_2O)	11 (55.0%)	11 (55.0%)
WBC/mm^3, median	8.5	4.5
Protein content, mg/dl, median	60	55
Glucose ratio, CSF/blood, %, mean	30.4±12.6	36.8±13.5
Positive India-ink preparation	20 (100%)	20 (100%)

WBC = white blood cell.

Table 3
Comparison of clinical variable between patients in the treatment group and the control group.

Variable	Treatment group	Control group	p
Negative CSF culture for *C. neoformans*			
At 2nd week of treatment[a]	11/15 (73.3%)	16/20 (80.0%)	0.70
At 10th week of treatment[b]	14/14 (100%)	18/18 (100%)	-
Time until normal body temperature after treatment, d, mean	7.2 ± 0.6	7.4 ± 0.6	0.41
Death	6 (30.0%)	2 (10.0%)	0.24
Persistence of high CSF pressures at the 10th week of treatment[b]	6/14 (42.8%)	7/18 (38.9%)	0.59

[a]Excluded in this category are 5 patients who died within 2 weeks of treatment in the treatment group.
[b]Excluded in this category are 6 patients who died in the treatment group and 2 patients who died in the control group.

The results of treatment are summarized in Table 3. There were not significant differences between the groups in regard to the negative CSF cultures for *C. neoformans* in the 2nd and 10th weeks of treatment, time until normal body temperature after treatment, number of patients who died, and persistence of high CSF pressure after completion of treatment. Of the 6 patients who died in the treatment group, 2 cases died on the 1st day of treatment, and the others died on the 6th, 11th, 13th and 30th days of treatment, respectively. Two patients who died in the control group; they died on the 20th and 36th days of treatment, respectively. All 5 patients in the treatment group who died within 2 weeks of treatment had elevated intracranial pressures, producing brain herniation. The 3 patients who died after 2 weeks of treatment (1 in the treatment group and 2 in the control group) developed acute progressive deterioration of consciousness before death. No hepatitis was seen in the treatment group.

DISCUSSION

In an *in vitro* study, the combination of amphotericin B and rifampin produced a greater effect on the reduction of the MIC of amphotericin B, than when either drug was used individually, for *C.neoformans*. The mechanism for this was hypothesized to be that the amphotericin B altered the permeability barrier of the cytoplasmic membrane of the pathogen, allowing increased penetration of rifampin, which in turn inhibited fungal RNA polymerase (Srimuang *et al*, 2000). The results of our study showed the combination of amphotericin B and rifampin is not superior to amphotericin B alone for an initial treatment of cryptococcal meningitis. Elevated intracranial pressure was an important factor in the clinical outcome (Denning *et al*, 1991). In our study, although we performed frequent lumbar punctures in patients with increased CSF pressure, brain herniation still occurred. Early ventricular or lumbar shunting may be helpful to prevent this complication. Further research is needed to prove this postulation.

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