

INITIAL TREATMENT WITH AMPHOTERICIN B PLUS RIFAMPIN IN THE ACUTE TREATMENT OF CRYPTOCOCCAL MENINGITIS IN AIDS

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Abstract. The result of initial treatment with amphotericin B (0.7 mg/kg/day) plus rifampin (600 mg/day) for 2 weeks, followed by fluconazole (400 mg/day) for 8 weeks in the acute treatment of cryptococcal meningitis in AIDS is reported. There were 10 patients in the study: at 2 weeks, all had made a clinical response and cerebrospinal fluid was sterile in 4 patients; at 10 weeks, all had negative cerebrospinal fluid cultures. Serious side effects were not detected.

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/day), with or without flucytosine, for 2 weeks followed by fluconazole (400 mg/day) for 8 weeks or until cerebrospinal fluid (CSF) cultures are sterile (van der Horst *et al*, 1997). The result of this regimen was that a clinical response was seen in 83% of patients after two weeks and that the CSF cultures were negative in 51% and 72% of cases within two weeks and ten weeks of commencement of treatment respectively. There remained, therefore, the problem of patients who failed of to respond.

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). This report gave a result of initial treatment with amphotericin B plus rifampin in the acute treatment of cryptococcal meningitis in AIDS, which to our knowledge, was not previously documented.

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) were studied. A positive test for the HIV antibody and a positive CSF culture for *C. neoformans* confirmed HIV infection and cryptococcal meningitis respectively.

Patients were excluded if they had: a known allergy to either drug; a white cell count under $1,500/\text{mm}^3$, a platelet count under $30,000/\text{mm}^3$, significant impairment of liver ($>5 \times$ normal) or renal function (creatinine $>3 \mu\text{g}/\text{mm}^3$); another acute opportunistic infection or tuberculosis or 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.

Treatment

The treatment regimen included amphotericin B (0.7 mg/kg/day) plus rifampin (600 mg/day) for the initial two weeks of therapy, followed by fluconazole (400 mg/day) for eight

Table 1
Baseline characteristics of the study patients.

Characteristics	
No. of patients	10
Age in years	29.4 (25-35)
No. of males	4
Signs/Symptoms	
Headache	10
Fever (T \geq 38.0°C)	6
Meningismus	8
Confusion	1
CSF abnormalities	
High opening pressure (\geq 300 mm H ₂ O)	7
WBC/mm ³	38.2 (0-160)
Protein content, mg/dl	99.7 (41-235)
Glucose ratio, CSF/blood	30.6 (12-40)
Positive India-ink preparation	10

Note. Data are no. of patients or mean (range). T, temperature.

weeks. Repeat lumbar punctures were performed for patients who had CSF pressure \geq 300 mm H₂O.

Evaluation

After a baseline evaluation, the patients' conditions were evaluated every day for the first 2 weeks and thereafter monthly until the 10-week study period was completed. Studies of CSF were conducted at base line and at weeks 2 and 10. Cultures of the fungi were kept for 30 days before being discarded. Complete blood count, BUN, creatinine and liver function tests were also performed.

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.

Statistical analysis

The primary goal of this study was the determination of the efficacy of amphotericin B plus rifampin for the initial treatment of cryptococcal meningitis in patients with AIDS.

Information obtained from the subjects and laboratories was recorded on case-record forms. Data were analyzed by descriptive statistics.

RESULTS

From March 2000 until October 2000, 10 patients were enrolled in the study. The baseline characteristics of the patients are shown in Table 1. The mean duration of fever and headache was 18.5 days (range 1-60 days).

Outcome

At two weeks, all patients had made a clinical response and the CSF cultures were negative in four cases. All patients had negative cultures at ten weeks. No hepatitis was seen; five patients had acute anemia, requiring blood transfusion, which occurred during the first two weeks.

DISCUSSION

Our study is the first to demonstrate the good results of combining amphotericin B and rifampin for the initial treatment of cryptococcal meningitis in patients with AIDS. The

mechanism of the drugs was hypothesized to be that amphotericin B altered the permeability of the cytoplasmic membrane of the pathogen, allowing increased penetration of rifampin, which in turn inhibited the fungal RNA polymerase (Srimuang *et al*, 2000). We can not precisely explain finding that, at two weeks, the percentage of CSF sterility was similar to that of the previous study, although at ten weeks all patients had sterile CSF. The combination of amphotericin B and rifampin may have a delayed effect on the organisms.

The result of this study suggests that the combination of amphotericin B and rifampin is promising as an initial treatment for cryp-

tococcal meningitis. Further study is necessary to prove the efficacy of this regimen compared with the currently recommended approach.

REFERENCES

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