

## Use of High-Dose Fluconazole as Salvage Therapy for Cryptococcal Meningitis in Patients with AIDS

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**Eight patients with AIDS were treated orally with 800 mg of fluconazole daily for cryptococcal meningitis for a mean duration of 4.5 months. Previous antifungal treatment had failed for all of the patients. No major toxicity was observed. Three patients died from cryptococcal infection. High-dose fluconazole may be effective salvage therapy for cryptococcal meningitis.**

Cryptococcal meningitis is a life-threatening infection in patients with AIDS. Cryptococcal disease accounts for 5 to 10% of all opportunistic infections in patients with AIDS (5-7). Even with standard therapy, the relapse rate of this fungal infection in patients with AIDS is high, approaching 34% within 4 months (2, 6). Thus most patients are given suppressive therapy to help control the infection, but relapses still occur (9, 10, 12).

The triazole fluconazole has shown promise in the treatment of cryptococcal meningitis, and it appears to be better tolerated than amphotericin B. Fluconazole has several practical advantages over amphotericin B; it can be given orally or intravenously, and because it has a long half-life, fluconazole can be taken once a day. Fluconazole also has excellent penetration in cerebrospinal fluid (CSF), approaching 80% of that attained in serum (1, 3). The drug is well tolerated, with infrequently seen adverse effects such as headache, nausea, vomiting, skin rash, and diarrhea (8).

We encountered eight patients for whom primary antifungal therapy had failed or who had relapses after that therapy. We wished to learn whether 800 mg of oral fluconazole was effective and well tolerated as salvage therapy. The decision to change therapy to high-dose fluconazole therapy was left to the discretion of the physicians managing the individual cases. Reasons to change therapy were commonly based on clinical deterioration in addition to unchanged or increasing cryptococcal antigen titers in CSF.

Hospital and human immunodeficiency virus clinic records were reviewed. The mean age of the patients was 34.5 years. All eight were males with documented human immunodeficiency virus infection. Cryptococcal meningitis was the first opportunistic infection in four patients. Other antifungal therapy had failed for all patients prior to the initiation of high-dose fluconazole therapy. Antecedent treatment had been given to seven patients for a mean of 21 weeks (3 to 40 weeks). Such therapy for all eight patients included amphotericin B for six patients, amphotericin B lipid complex for one patient, SCH 39304 for three patients (200 mg/day itraconazole for 1 patient (400 mg/day), and fluconazole for three patients (200 to 400 mg/day). Four of the eight patients had received more than one antifungal drug before starting high-dose fluconazole therapy.

Patients were given 800 mg of oral fluconazole daily for a mean of 4.5 months (1.5 to 9 months) on a compassionate

basis for salvage therapy. Since these patients were already in the hospital for management of their cryptococcal disease, the initial course of high-dose fluconazole was started in the hospital. Once their conditions were considered to be stable, the patients were monitored on an outpatient basis. Their individual characteristics and outcomes are noted in Table 1. Patients were not tested for resistance to fluconazole.

Seven patients died. Two deaths (patients 1 and 2) were due to complications from Kaposi's sarcoma and lymphoma. These two patients had negative CSF cultures prior to their demise. Two patients (patients 3 and 7) died from wasting syndrome. There was no clinical evidence of active disease, and CSF cultures were negative. Patient 3 was initially started on amphotericin B (0.5 mg/kg of body weight per day) when he presented with headaches, nausea, vomiting, and diplopia. His initial cryptococcal antigen titer in CSF was elevated at 1:1,024 despite negative CSF cultures. After 3 weeks of amphotericin B therapy he remained symptomatic, with a persistently high cryptococcal antigen titer of 1:1,024 in CSF but negative CSF cultures. Because of his lack of clinical improvement, his amphotericin B therapy was discontinued and he was placed on 800 mg of oral fluconazole daily. Headaches improved within 4 weeks of high-dose fluconazole therapy. After 20 weeks of therapy, his titer declined to 1:256. His dose of fluconazole was then decreased to 400 mg daily for maintenance. He remained on that dose for 12 months and was clinically stable for that period of time. However, in September 1991, he developed *Staphylococcus aureus* sepsis secondary to an ankle infection. Although he recovered from this bacterial infection, he became more debilitated and anorexic. A lumbar puncture performed within a month of his demise revealed a negative CSF culture and a cryptococcal antigen titer of 1:4 in CSF.

Patient 7 developed erythema multiforme while on fluconazole. However, he was also taking several other drugs, including trimethoprim-sulfamethoxazole. Therapy with both fluconazole and trimethoprim-sulfamethoxazole was stopped, and 3 weeks later, when the skin lesions were healed, fluconazole therapy was resumed without problems. The patient continued to receive fluconazole, and later the dose was decreased to 400 mg orally a day for 4 months until the patient died of wasting syndrome. Blood and CSF cultures within a month of his demise were negative.

Three patients died, probably from complications related to cryptococcal disease. Patient 4 had been on high-dose fluconazole for 4 months. At the time of his death he had an increasing cryptococcal antigen titer in CSF, and crypto-

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TABLE 1. Patient characteristics<sup>a</sup>

Patient	Result before treatment		Result after treatment		Duration of treatment with 800 mg (wks)	Outcome
	Antigen <sup>b</sup> titer in CSF	CSF culture	Antigen <sup>b</sup> titers in CSF	CSF Culture		
1	1:512	Positive	1:512	Negative	8	Dead, with Kaposi's sarcoma and lymphoma
2	1:64	Positive	1:64	Negative	36	Dead, with Kaposi's sarcoma
3	1:1,024	Negative	1:256	Negative	20	Dead, with wasting syndrome
4	1:32	Positive	1:256	Positive	28	Dead, with cryptococcal infection
5	1:256	Positive	1:256	Negative	8	Dead, with cryptococcal infection
6	1:1,024	Positive	1:64	Negative	10	Alive on 400 mg of fluconazole
7	1:1,024	Positive	1:256	Negative	32	Dead, with wasting syndrome
8	1:1,024	Positive	1:1,024	Positive	6	Dead, with cryptococcal infection

<sup>a</sup> Patients were treated with fluconazole.

<sup>b</sup> Cryptococcal antigen.

cocci were repeatedly isolated from the CSF. Patient 5 had been receiving SCH 39304 for 3 months, with no response. Lumbar punctures on a bimonthly basis showed persistent cryptococcal antigen titers of 1:256 in CSF and CSF cultures positive for cryptococcal infection. He was placed on 800 mg of fluconazole and initially improved clinically. Although his CSF cultures became negative his cryptococcal antigen titer in CSF remained unchanged at 1:256 2 months into treatment with 800 mg of oral fluconazole daily. Six weeks into therapy, he developed cranial nerve abnormalities and a decrease in mental health. Computerized axial tomography of the head showed a ring-enhanced lesion near the fourth ventricle, with obstruction. A lumbar puncture was not performed because of the possibility of herniation. The patient was empirically placed on toxoplasmosis therapy, but without success. An autopsy was not performed.

Patient 8 did not respond to any therapy for cryptococcal meningitis. He was initially placed on SCH 39304 for 5 months and was then switched to amphotericin B lipid complex for 1 month because of a lack of clinical improvement. He did not respond and so was placed on 800 mg of oral fluconazole daily. The patient remained symptomatic, with intermittent fevers and headaches. After 2 months, the fluconazole was discontinued and amphotericin B therapy was begun. He still showed no clinical response. His CSF cultures remained positive for cryptococcal infection, and his antigen titers were persistently elevated to 1:1,024 in CSF. He ultimately expired from cryptococcal disease.

Patient 6 was initially placed on 200 mg of oral fluconazole daily for a cryptococcal antigen titer of 1:4 in serum. He had been complaining of weight loss, and the workup was significant only for the cryptococcal antigen titer in serum. His blood and CSF cultures were negative, and his cryptococcal antigen titer in CSF was negative. His condition remained stable until 5 months later, when he began to complain of headaches. A lumbar puncture revealed a cryptococcal antigen titer of 1:1,024 in CSF, and cryptococci grew in CSF culture. He was placed on 800 mg of fluconazole daily for 10 weeks, with resolution of his headache. He has remained on 400 mg of oral fluconazole for 12 months and is clinically stable, without evidence of cryptococcal infection.

Cryptococcal meningitis in patients with AIDS remains a frustrating problem. There are limited therapeutic options, and treatment is not always effective. There are no clear guidelines on how to manage these patients. Amphotericin B remains the drug of choice for acute cryptococcal meningitis, but this antifungal agent can be toxic. It can be combined

with flucytosine, but flucytosine can also be toxic, especially if elevated levels accrue as a result of renal insufficiency caused by the amphotericin B. One study concluded that the addition of flucytosine to amphotericin B did not prolong survival of patients with AIDS (5). Although this regimen may be effective, it is highly toxic and may become more difficult if it is used on a long-term basis.

The use of fluconazole as suppressive therapy for cryptococcosis in patients with AIDS has already been investigated (10, 11). One study reported that two of nine patients on maintenance fluconazole had relapses with doses of no more than 200 mg daily (11). This study examined the possibility of raising the dose of fluconazole to 800 mg daily for suppressive therapy. This noncomparative retrospective review indicates that up to 800 mg of oral fluconazole taken daily is well tolerated and also suggests that this regimen is beneficial to at least some patients. However, the failure of the therapy for three patients indicates that, like all other regimens to date, high-dose fluconazole is less than ideal and that further improvements are needed.

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