High-Dose Fluconazole Therapy for Cryptococcal Meningitis in Patients with AIDS

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Fluconazole (800–1,000 mg iv) was administered to 14 consecutive patients with AIDS and cryptococcal meningitis. At 10 weeks the rate of clinical success was 54.5% (six of 11 patients responded to fluconazole); the Kaplan-Meier estimate of the response rate was 67.1%, and the overall mortality rate was 18.2% (two of 11 patients died). At the end of treatment, eight (72.7%) of 11 patients responded to fluconazole. The median time to the first negative cerebrospinal fluid (CSF) culture was 33.5 days (95% confidence interval, 18.3–67.3); the median time for patients with initial CSF cryptococcal antigen titers of ≥1:1,024 was 66 days compared with 18 days for patients with initial CSF cryptococcal antigen titers of <1:1,024 (P = .06). The median time to the first negative CSF culture for patients with an isolate for which the minimum inhibitory concentration (MIC) was 4 μg/mL was 56 days compared with 16 days for patients with an isolate for which the MIC was <4 μg/mL (P = .11). The mean serum and CSF levels of fluconazole at steady state were 42.47 ± 26.31 μg/mL and 36.63 ± 21.08 μg/mL, respectively (ratio of CSF:serum, 0.86). No treatment was interrupted and no dose was tapered because of side effects. High-dose fluconazole might be an effective and well-tolerated therapeutic option for patients with AIDS and acute cryptococcal meningitis.

Results

The baseline characteristics of 14 patients with AIDS and confirmed cryptococcal meningitis are summarized in table 1. Three patients were excluded from the efficacy analysis: one was lost to follow-up, and two were treated with amphotericin B and fluconazole from the beginning.

At 10 weeks the rate of clinical success was 54.5% (six of 11 patients responded to fluconazole); the response rate determined by the Kaplan-Meier estimate of the time to the first negative CSF culture was 67.1% (figure 1), and the overall mortality rate was 18.2% (two of 11 patients died). Primary therapy failed for five patients (45.5%). Two patients died before completing 10 weeks of therapy; both had sterile CSF, but their autopsies revealed disseminated cryptococcosis. One patient’s therapy was shifted to amphotericin B because of a lack of response after 21 days of fluconazole treatment; this patient’s condition improved. The CSF of two patients, although their conditions clinically improved, became sterile after 10 weeks of treatment, on days 77 and 112, respectively. At the end of treatment, the overall response rate to high-dose with persistently positive cultures that required any modification of the primary therapy or if the patient died early (<10 weeks) of cryptococcosis. CSF and serum levels of fluconazole were measured simultaneously at steady state (after ≥2 weeks of therapy) by HPLC that was modified by a previously described method [6]. MICs of fluconazole were determined by a broth microdilution test [7].

Cryptococcal meningitis is the most common life-threatening fungal infection in patients with AIDS; however, current therapeutic options seem to be suboptimal because of poor efficacy or toxic effects [1–4]. High-dose fluconazole therapy might be a different approach [5]. We postulated that higher CSF levels of fluconazole early in the course of treatment of cryptococcal meningitis, resulting from higher dosages (800–1,000 mg/d), might be associated with more-rapid CSF sterilization and a better clinical outcome.

Patients and Methods

After obtaining informed consent, we used fluconazole (800–1,000 mg/d) for 3 weeks iv then orally to treat consecutive patients who had AIDS and suspected cryptococcal meningitis. CSF analysis was done at baseline and then every 2 weeks; high-dose fluconazole therapy was continued until the CSF culture became negative or for no less than 4 weeks. Treatment was considered to have failed if the patient had clinically stable disease or progressive clinical deterioration with persistently positive cultures that required any modification of the primary therapy or if the patient died early (<10 weeks) of cryptococcosis. CSF and serum levels of fluconazole were measured simultaneously at steady state (after ≥2 weeks of therapy) by HPLC that was modified by a previously described method [6]. MICs of fluconazole were determined by a broth microdilution test [7].

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Informed consent was obtained from the patients or their parents or guardians, and the guidelines on human experimentation of the authors’ institutions were followed in the conduct of the clinical research.

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Table 1. Baseline clinical and laboratory features of patients with AIDS and cryptococcal meningitis.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>14</td>
</tr>
<tr>
<td>Median age in y (range)</td>
<td>36 (27–70)</td>
</tr>
<tr>
<td>No. (%) of males</td>
<td>11 (78.6)</td>
</tr>
<tr>
<td>Mean no. of CD4 cells/mm³ (range)</td>
<td>38 (3–85)</td>
</tr>
<tr>
<td>No. (%) with positive* blood cultures</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>No. (%) with positive* cultures of specimens from an extraneural site</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>No. (%) with abnormal CSF opening pressure (&gt;18 cm H2O)</td>
<td>10 (71.4)</td>
</tr>
<tr>
<td>No. (%) with CSF WBC count of &lt;20/mm³</td>
<td>10 (71.4)</td>
</tr>
<tr>
<td>No. (%) with CSF cryptococcal antigen titer of ≥1:1,024</td>
<td>7 (50)</td>
</tr>
<tr>
<td>No. (%) with serum cryptococcal antigen titer of ≥1:1,024</td>
<td>9 (64.3)</td>
</tr>
<tr>
<td>No. (%) with abnormal sensorium (lethargy or obtundation)</td>
<td>3 (21.4)</td>
</tr>
</tbody>
</table>

* Positive for Cryptococcus neoformans.

Flucytosine therapy increased to 72.7%, as the conditions of eight of 11 patients eventually improved.

The median time to the first negative CSF culture was 33.5 days (95% CI, 18.3–67.3). All CSF cultures were negative for cryptococci by day 112. The median time to the first negative CSF culture for patients with initial CSF cryptococcal antigen titers of ≥1:1,024 was 66 days compared with 18 days for patients with initial CSF cryptococcal antigen titers of <1:1,024 (P = .06) (figure 2). Serum and CSF levels of fluconazole at steady state were determined simultaneously in 12 patients on 22 occasions; the mean levels were 42.47 ± 26.31 µg/mL and 36.63 ± 21.08 µg/mL, respectively (ratio of CSF: serum, 0.86). MICs of fluconazole for the 14 cryptococcal isolates were <0.125 µg/mL for 3 strains, 1 µg/mL for 1 strain; 2 µg/mL for 1 strain, and 4 µg/mL for 9 strains. The median time to the first negative CSF culture for patients with an isolate for which the MIC was 4 µg/mL was 56 days compared with 16 days for patients with an isolate for which the MIC was <4 µg/mL (P = .11).

No treatment was interrupted and no dose was tapered because of side effects. Eleven (68.8%) of 16 patients had hematologic toxic effects; four patients had hepatic toxic effects.

**Discussion**

The clinical and mycologic response, the median time to CSF sterilization, and the mortality rate associated with cryptococcal meningitis among our patients compared favorably with those among patients receiving treatment with amphotericin B or lower doses of fluconazole (200–400 mg) [1, 2] and are similar to those reported in studies of fluconazole (400 mg/d) combined with flucytosine [3] and oral fluconazole (800 mg/d) [8].

The favorable outcome we observed was probably not related to selection of patients with good prognoses because all patients...

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Kaplan-Meier estimates of the time to the first negative CSF culture for patients with AIDS and cryptococcal meningitis. The median time was 33.5 days (95% CI, 18.3–67.3)

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Correlation between baseline CSF cryptococcal antigen titer and time to CSF sterilization for patients with AIDS and cryptococcal meningitis. Solid lines = patients with CSF cryptococcal antigen titers of ≥1:1,024; dotted lines = patients with CSF cryptococcal antigen titers of <1:1,024 (P = .06, logrank test for the difference between the groups).
presented at baseline with one or more of the major factors predictive of death during therapy [1, 9]. The high CSF levels resulting from 800-mg to 1,000-mg doses of fluconazole may have accounted for the faster CSF sterilization and the better outcome observed. Baseline CSF cryptococcal antigen titers of $\geq 1:1,024$ seem to be reliable pretreatment predictors of slow CSF sterilization. The MICs for cryptococcal isolates (from $<0.125$ to $4 \mu g/mL$) that we found were similar to those already reported [10] and were well below the range of CSF levels resulting from high-dose fluconazole therapy. According to the recently suggested direct relationship between high MICs and the rate of failure of fluconazole treatment of cryptococcal meningitis in patients with AIDS [11], we observed a trend: the CSF of patients with cryptococcal isolates for which the MIC is high become sterile slower.

As in previously reported small series of treated patients [5, 8], high-dose fluconazole therapy was well tolerated, and no treatment had to be interrupted and no dose had to be tapered because of side effects. The toxic effects of high-dose fluconazole therapy compared favorably with those of a treatment regimen including amphotericin B or flucytosine [1, 3].

This trial suggests that high-dose fluconazole therapy might be an effective and well-tolerated option in the primary treatment of acute cryptococcal meningitis in patients with AIDS. However, further clinical investigation of this therapeutic approach should take into account the recently described favorable results of a 2-week treatment course of amphotericin B or flucytosine [12].

References