

Fluconazole alone or combined with flucytosine for the treatment of AIDS-associated cryptococcal meningitis

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An all oral treatment for cryptococcal meningitis is attractive, particularly where amphotericin B use is impractical. Both fluconazole and flucytosine are available in oral formulations and have activity against *Cryptococcus neoformans*. We conducted a prospective phase II dose escalation study employing doses of fluconazole ranging from 800 to 2000 mg daily for 10 weeks used alone or combined with flucytosine at 100 mg/kg per day for the first 4 weeks. We found that increasing doses of fluconazole were associated with an increase in survival and a decrease in the time to conversion of the cerebrospinal fluid from culture positive to culture negative. Addition of flucytosine to fluconazole improved outcomes in each dosing cohort. High doses of fluconazole alone or combined with flucytosine were well tolerated.

Keywords *Cryptococcus neoformans*, meningitis, AIDS, fluconazole, drug treatment, flucytosine

Introduction

Cryptococcal meningitis is a common clinical problem among those with AIDS accounting for up to one third of the deaths in many parts of the developing world [1–6]. Treatment with amphotericin B, the drug of choice for this infection, is difficult because of the need to establish and maintain intravenous access, monitor and treat acute infusion-related reactions and cumulative drug associated toxicities [7]. These difficulties often make the use of amphotericin B prohibitively costly. In contrast, fluconazole is widely available, inexpensive, can be given orally and has demonstrated effectiveness against *Cryptococcus neoformans* [8–11]. Flucytosine is also an orally available agent with activity against *C. neoformans* but because of the rapid emergence of drug resistance has been relegated to use in combination with other drugs [8,12]. The present study reports our experience with high doses of fluconazole given alone or combined with flucytosine.

Methods

The study was approved the Institutional Review Boards at each participating center. Eighty-nine subjects with their first episode of cryptococcal meningitis and documented with the human immunodeficiency virus (HIV) were enrolled in the clinical trial between November 1991 and March 1994. Written informed consent was obtained from the subject or their legally authorized representative. Subjects were excluded from participation if they had major psychiatric diseases, severe liver or renal disease, were receiving rifampin, were pregnant or nursing, were unlikely to survive for two weeks or had received more than three days of antifungal therapy for this infection. Four dosing cohorts were employed with subjects randomly allocated between treatment assignments within a cohort. Fluconazole was given at the assigned dose for 10 weeks, and the flucytosine dose of 100 mg/kg daily in four divided doses was given for the first 4 weeks.

Cohort 1: fluconazole @ 800 mg with/without flucytosine and 1200 mg of fluconazole alone.

Cohort 2: fluconazole @ 1200 mg with/without flucytosine and 1600 mg fluconazole alone.

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Cohort 3: fluconazole @ 1600 mg with or without flucytosine.

Cohort 4: fluconazole @ 2000 mg with or without flucytosine.

Cerebrospinal fluid (CSF) was scheduled to be sampled at 2, 4, 6 and 10 weeks unless the previous sample was negative. A successful outcome was defined as being alive with a single negative cerebrospinal fluid culture for *C. neoformans* on or before week 10 employing the assigned study therapy. Comparisons were made with a Fisher's exact test for categorical variables.

Results

The baseline demographics of that study population are presented in Table 1. All were proven to be infected with HIV and none had significant impairment of cognition, e.g., lethargy or coma. In general, the subjects who received flucytosine tended to have more severe infection based upon median values of the CSF cryptococcal latex agglutination antigen titer but this did not reach statistical significance. The composite 10-week overall response rates (success defined as alive and CSF culture negative) for fluconazole with and without flucytosine are given in Table 1. Of note, fluconazole alone at the highest doses (1600 mg and 2000 mg/day) had clinical success rates over 60%. As the dose level of fluconazole was increased, there was an incremental increase in response ($P < 0.02$, log rank test). At each dose level of fluconazole (except 1600 mg dosing of fluconazole), the addition of flucytosine to the fluconazole improved the overall response rates ($P < 0.02$, log rank test). Thus, there was a two way interaction between the fluconazole and flucytosine with higher doses of fluconazole associated with an improved response and the addition of flucytosine to

fluconazole improving response ($P < 0.05$, logistic regression). The overall success was 75% for subjects that received the combination of fluconazole and flucytosine. No relapses were observed during follow-up among those subjects deemed successful at 10 weeks.

As expected, symptoms were commonly observed, but rates did not appear to differ, between treatment groups (Table 2). Nausea and vomiting were common clinical complaints, particularly early in the course of therapy. Often it was necessary to alter the oral dosing frequency of fluconazole to twice or four times daily to minimize the feeling of nausea. Only one subject required prolonged intravenous use of fluconazole, ultimately tolerating oral therapy 2 weeks into treatment. One subject withdrew from the study because of a brief episode of vomiting. Changes in skin color, alopecia and complaints of dry skin were observed in 34 (38%) subjects. Skin pigmentation and dry skin complaints slowly resolved once lower doses of fluconazole were employed.

Of note, liver enzyme abnormalities were uncommon – exceeding 1.5 times the upper limit of normal in only 2% of those given fluconazole alone and only 7% employing combination therapy. Granulocytopenia (18% vs. 7%) and thrombocytopenia (4% vs. 0%) were increased in those on flucytosine compared to on fluconazole only, were managed by a 50% reduction in the dose of flucytosine and were not associated with episodes of infection or bleeding.

Three noteworthy clinical events occurred that may have been associated with higher dose fluconazole use. One subject receiving warfarin experienced a lethal bleeding event after a dosing error with warfarin. Two subjects had cranial venous thrombosis (one sagittal sinus and one lateral sinus thrombosis) while receiving only fluconazole at doses of 800 and 1200 mg daily. Both had normal protein S and C levels and normal

Table 1 Baseline demographic information and overall outcome.

	Fluconazole alone				Fluconazole plus flucytosine			
	800	1200	1600	2000	800	1200	1600	2000
Dose (mg/kg-day)	800	1200	1600	2000	800	1200	1600	2000
Number of patients	9	16	16	8	8	8	16	8
Male	100%	94%	94%	100%	100%	100%	100%	100%
Median age	35	40	35	36	38	34	37	37
Median CD4 cells	8	36	33	35	25	29	11	47
Median CSF CrAg	1:1024	1:128	1:64	1:32	1:512	1:64	1:512	1:256
Minimum CrAg	1:2	Neg.	Neg.	Undil.	1:2	Neg.	1:2	1:2
Maximum CrAg	1:8192	1:65536	1:8192	1:4096	1:131072	1:32768	1:32768	1:8192
1st O.I.	56%	25%	44%	88%	38%	62%	44%	25%
Overall success	11%	37%	62%	62%	75%	87%	62%	75%

CD4 cells, CD4+ T lymphocytes count. Min. CrAg., Minimum CSF cryptococcal latex agglutination antigen titer. Max. CrAg., Maximum CSF cryptococcal latex agglutination antigen titer. Neg. Negative. Undil., Undilute. 1st O.I., first opportunistic infection. Success, clinical and microbiological, i.e., alive and CSF culture negative on or before week 10.

Table 2 Summary of toxicities.

Side effect	Fluconazole alone <i>n</i> (%)	Fluconazole plus flucytosine <i>n</i> (%)
Sweating	6 (12%)	6 (15%)
Tachycardia	7 (14%)	7 (18%)
Abdominal pain	8 (16%)	5 (12%)
Constipation	8 (16%)	6 (15%)
Diarrhea	10 (20%)	7 (18%)
Nausea	29 (59%)	23 (57%)
Vomiting	27 (55%)	24 (60%)
Weight loss	9 (18%)	8 (20%)
Anemia	7 (14%)	1 (3%)
Granulocytopenia (<500)	2 (4%)	7 (18%)
Thrombocytopenia (<50,000)	0	3 (7%)
Hepatic enzyme increase (1.5×)	1 (2%)	3 (7%)
Alopecia	6 (12%)	4 (10%)
Dry skin	9 (18%)	13 (32%)
Increased skin pigmentation	1 (2%)	1 (3%)
Decreased hearing	3 (6%)	5 (12%)

prothrombin and partial thromboplastin times. A causal association with the cranial venous thromboses and fluconazole could not be excluded. Both recovered with continued use of fluconazole.

Conclusion

Overall, fluconazole was well tolerated up to doses of 2000 mg daily and the maximum tolerated dose was not achieved. This study suggested that increasing the dose of fluconazole increases the overall efficacy of the drug. The addition of flucytosine to fluconazole was also beneficial without major increments in bone marrow, liver or gastrointestinal toxicity. Because fluconazole and flucytosine are active orally, this regimen is attractive for the treatment of cryptococcal meningitis where use of amphotericin B, which requires intravenous administration and careful monitoring of renal function and serum electrolytes and magnesium, is impractical or too costly. The ease of administration, the apparent safety and the observed levels of efficacy of the regimens all support continued evaluation of high dose fluconazole alone or combined with flucytosine as an alternative to amphotericin B alone or combined with flucytosine.

The limited size of this study does not preclude substantial rates of potentially serious and life-threatening drug interactions or drug toxicities, particularly cranial venous thrombosis which occurred twice. The

mechanism(s) that would lead to cranial venous thrombosis were not evident in the two subjects and they appeared to have normal coagulation parameters. Also, as evident by the lethal bleeding event, warfarin interacts with fluconazole potentiating its anticoagulant effects and thus should be used with caution in those receiving fluconazole.

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