REVIEWS OF INFECTIOUS DISEASES • VOL. 12, SUPPLEMENT 3 • MARCH-APRIL 1990
 0162-0886/90/1202-0044$02.00

Overview: Treatment of Cryptococcal Meningitis

Alan M. Sugar, John J. Stern, and Bertrand Dupont

From the Evans Memorial Department of Clinical Research and the Department of Medicine, Boston University Medical Center, Boston, Massachusetts; the Infectious Diseases Section, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and the Hospital and Mycology Unit, Pasteur Institute, Paris, France

Infections caused by *Cryptococcus neoformans* cause significant morbidity and high mortality, particularly among immunocompromised patients. Cryptococcal meningitis is an important cause of central nervous system disease and death in patients with AIDS. Although the introduction of amphotericin B has greatly improved the prognosis of patients with cryptococcal meningitis, 30 years of experience have revealed important clinical limitations, including modest efficacy, nephrotoxicity, other clinically significant toxicities, and the inconvenience of intravenous dosing. The discovery of the additive effects of amphotericin B and flucytosine in cryptococcosis resulted in some improvement in efficacy and reduction in amphotericin B–related toxicity. However, ~30% of patients with cryptococcal meningitis still fail to respond to therapy. Ketoconazole has not proved useful in treating cryptococcal meningitis. Accumulating evidence suggests that the antifungal triazoles fluconazole, itraconazole, and SCH 39304 represent an advance in the treatment of cryptococcal meningitis, particularly in AIDS patients. Preliminary clinical trials in patients with and without AIDS have indicated that fluconazole and itraconazole are effective and well tolerated as either initial or maintenance therapy. Two large comparative trials of fluconazole and amphotericin B in patients with cryptococcal meningitis (mostly those with AIDS) are under way.

Opportunistic infections caused by *Cryptococcus neoformans* are associated with a high incidence of morbidity and mortality, particularly among patients with impaired defense mechanisms [1, 2]. Before the clinical introduction of amphotericin B in the late 1950s, a diagnosis of cryptococcal meningitis carried with it a prognosis of certain death, reflecting the failure of such infections to resolve spontaneously [3, 4]. Even in the years when amphotericin B was used alone for the treatment of cryptococcal meningitis, cures were achieved in only slightly more than 50% of patients [5, 6].

Recently described as the most common form of fungal meningitis in the United States today [7], cryptococcal meningitis remains an important treatment challenge, especially in patients with AIDS. Although amphotericin B (alone or in combination with flucytosine) continues to be the standard therapeutic regimen, problems such as a relatively high failure rate, a high incidence of adverse reactions, and the inconvenience of intravenous dosing have led to a search for new antimycotic agents. This article reviews the experience with systemic antifungal therapies since the introduction of amphotericin B three decades ago, emphasizing the role of the azoles in the management of cryptococcal meningitis.

Please address requests for reprints to Dr. Alan M. Sugar, The University Hospital, E-540, 88 East Newton Street, Boston, Massachusetts 02118.

Clinical Experience with Amphotericin B

Among the many polyene antibiotics developed over the past 30 years, amphotericin B is the only one parenterally administered. It is also distinguished from other polyenes by its higher degree of binding to ergosterol, the mechanism by which it achieves its antifungal effect [8]. There is a dose-related separation between the fungistatic and fungicidal effects of amphotericin B [9]. The drug also appears to have pronounced immunoadjuvant activity [10–12]. In addition to the intravenous route, the intrathecal and intraperitoneal routes can be used for the administration of amphotericin B.

Amphotericin B has been used extensively since its introduction for the treatment of cryptococcal meningitis and numerous other systemic fungal infections. Although its efficacy remains unsurpassed, its initial promise as the first life-saving therapy for

cryptococcal meningitis has gradually been tempered by an appreciation of its therapeutic limitations as well as its significant toxicity. The most important adverse effect of amphotericin B is renal dysfunction, which occurs in ~80% of patients receiving the drug [13]. Other adverse reactions include chills, rigors, fever, headache, anemia, pulmonary edema, phlebitis, and seizures. Between 80% and 90% of patients receiving amphotericin B develop chills, and about 20% experience vomiting [14].

The glomerular filtration rate of virtually every patient treated with amphotericin B drops by ~40% soon after therapy is commenced, stabilizing at ~20%–60% of normal after multiple doses [14]. Although renal function returns almost to normal in most cases once the drug is stopped, the majority of patients who have undergone a full course of treatment experience a residual reduction in glomerular filtration [15]. In addition, patients treated with amphotericin B have been found to waste potassium and magnesium and sometimes develop renal tubular acidosis.

For the detection of potential renal toxicity and other toxicities related to the use of amphotericin B, patients should be monitored two or three times weekly during the first month and once a week thereafter until therapy is discontinued. Monitoring should include urinalysis and the measurement of serum creatinine, blood urea nitrogen, serum potassium and magnesium, bicarbonate, and hematocrit. Renal toxicity seems to be reduced or prevented by sodium repletion. Moreover, with the addition of flucytosine, efficacy can be maintained or improved with reduced doses of amphotericin B and a consequent decrease in toxicity.

Clinical Experience with Flucytosine

Flucytosine is a synthetic oral antimycotic agent that is particularly effective in certain well-defined clinical situations. In vivo studies in experimental murine models of infection have demonstrated activity against *C. neoformans* [16–18]. In common with amphotericin B, flucytosine shows dose- and time-dependent fungistatic and fungicidal activity.

Flucytosine is generally well tolerated, even when administered in high doses for extended periods. However, bone marrow suppression with the development of anemia, leukopenia, or thrombocytopenia is common [15, 19, 20]. Adverse gastrointestinal effects include nausea, vomiting, diarrhea, and (rarely) severe enterocolitis. Drug-induced hepatitis also has been reported.

Many of the adverse reactions associated with flucytosine therapy, and particularly the hematologic effects, occur when serum concentrations of the drug exceed 100 μg/mL [21]. This effect is especially apparent when flucytosine is administered in combination with amphotericin B, since amphotericin B–induced renal impairment results in an increase in serum concentrations of flucytosine. Thus, it is of critical importance to monitor serum concentrations of flucytosine (particularly in patients with renal dysfunction) and to keep peak serum levels well below 100 μg/mL [22, 23]. One problem in achieving this goal is that laboratory results are often delayed by several days, during which time the patient's serum flucytosine concentrations may exceed the desired level. For this reason, efforts must be made to obtain more rapid results.

Naturally resistant fungal strains are found among flucytosine-sensitive species, including 1%–2% of strains of *C. neoformans* [24]. In addition, the development of resistance to flucytosine during therapy in as many as 30% of patients with cryptococcosis [25] greatly limits the usefulness of flucytosine as monotherapy and provides a rationale for its use in combination with amphotericin B.

Combination Therapy with Amphotericin B and Flucytosine

In vitro [26, 27] and in vivo [18] evidence of the additive effects of amphotericin B and flucytosine in cryptococcosis led to clinical trials designed to evaluate the safety and efficacy of this combination in the treatment of cryptococcal meningitis. The results of one prospective but uncontrolled study in 15 patients with cryptococcal meningitis, which was completed in the mid-1970s, showed that eight patients (53%) treated with amphotericin B and flucytosine were cured within 8–34 months of the initiation of therapy [28]. Three patients (20%) died of cryptococcal meningitis; four died of other causes within 11 months of completing treatment. There were no relapses.

In a subsequent multicenter prospective study, Bennett et al. compared amphotericin B alone with amphotericin B plus flucytosine in 78 patients with cryptococcal meningitis, 66 of whom completed assessable courses of therapy [29]. The patients were randomly assigned to one of two groups: 10 weeks

of treatment with amphotericin B alone (0.4 mg/[kg·d] for 42 days, followed by 0.8 mg/kg every other day for 28 days) or 6 weeks of treatment with amphotericin B (0.3 mg/[kg·d]) and flucytosine (150 mg/[kg·d] divided into four daily doses). Some flexibility in dosing and duration of treatment was permitted according to stipulated criteria. As can be seen in table 1, the results of this trial favored combination therapy. When both protocols were adhered to, significantly more patients in the combination group than in the amphotericin B alone group improved or were cured (67% vs. 41%; $P < .05$). The results were similar when patients with courses not adhering to the protocol were included.

Lower doses of amphotericin B can be used effectively when the drug is combined with flucytosine. However, it has not yet been clearly determined whether higher doses of amphotericin B (e.g., 0.5 or 0.6 mg/[kg·d]) in combination with flucytosine are more effective than the standard dose used in the study just described (e.g., 0.3 mg/[kg·d]). However, flucytosine toxicity may be increased because of amphotericin B–induced renal dysfunction.

Of particular note is the fact that the incidence of nephrotoxicity was significantly lower ($P < .05$) in the combination treatment group than in the amphotericin B alone group. There were also significantly more rapid ($P < .001$) sterilization of the CSF in the combination group and significantly fewer deaths (24% vs. 47%; $P < .05$). However, nearly 30% of patients did not respond to combination therapy. Thus, although combination therapy appears to be more effective than amphotericin B alone, the success rate cannot be considered optimal.

Dismukes et al. [7] reported on a multicenter, prospective, randomized trial almost a decade after the study by Bennett and associates; in this study the efficacy and toxicity of 4 weeks vs. 6 weeks of combination therapy with amphotericin B plus flucytosine were compared. One hundred ninety-four patients with cryptococcal meningitis were enrolled in the study by 17 institutions over a 4 ½-year period. Initially, all patients received 28 days of treatment with intravenous amphotericin B (0.3 mg/[kg·d]) and oral flucytosine (150 mg/[kg·d], divided into equal doses given every 6 hours). At the end of this time, patients were eligible for randomization if they (*1*) adhered to the protocol, (*2*) had two negative blood and CSF cultures on treatment days 14 and 21, and (*3*) were in an alert and wakeful state.

Of the 91 patients who met the criteria for randomization, 46 were assigned to the group that received an additional 2 weeks of treatment (at the same dosages used during weeks 1–4), and 45 patients (the "4-week" group) received no further treatment. Patients also were characterized before randomization as either low or high risk; the latter group included organ transplant recipients, patients with non-Hodgkin's lymphoma, and patients with a pretreatment blood culture positive for *C. neoformans*.

Although 23 patients who had received organ transplants adhered to the initial 4-week protocol, most were not randomized after the first year of the study because four of the five patients initially assigned to the 4-week group relapsed. Subsequently, 18 recipients of organ transplants received 6 weeks of therapy.

Among the 91 nontransplantation patients ran-

Table 1. Therapy with amphotericin B vs. that with amphotericin B plus flucytosine for cryptococcal meningitis.

	No. of patients with outcome			
	Adherent		Inadherent	
Status*	Amphotericin B	Amphotericin B/flucytosine	Amphotericin B	Amphotericin B/flucytosine
Cured	7	13	3	2
Improved	4	2	1	5
Relapsed	5	1	0	0
Failed (full course)	6	2	0	0
Died during therapy	5	5	1	3
Proportion cured or improved	11/27	15/24	4/5	7/10

NOTE. Table is reprinted with permission from the *New England Journal of Medicine* [29].

* Patients considered cured had no evidence of active cryptococcosis on examinations including lumbar puncture at least 1 year after therapy. Those considered improved were discharged with cultures negative for *C. neoformans* and had no evidence of active cryptococcosis when last seen; however, the last examination was performed <1 year after therapy, the examination 1 year after therapy was incomplete, or the patient died of other causes within 1 year after therapy. Those defined as relapsed were discharged as improved but on readmission had *C. neoformans* isolated from CSF or urine. Those in whom a full course of therapy failed had positive cultures during the last 2 weeks of therapy or were retreated at the end of the course for presumed therapeutic inadequacy. Those who died during therapy died of any cause during the same admission that protocol therapy was given.

domized to treatment, 60 (66%) were cured, 13 (14%) improved, and 18 (20%) relapsed. While the estimated relapse rates for the 4-week and 6-week regimens were 27% and 16%, respectively, the difference was not statistically significant, and the predetermined risk stratification (high and low groups) did not correlate significantly with outcome (table 2).

The overall efficacy of the amphotericin B plus flucytosine combination can be appreciated through a consideration of the outcomes of all 194 patients enrolled in the study, as all were initially given the same treatment regimen. In addition to the 18 relapses among the randomized nontransplantation patients, seven relapses occurred among the 23 transplant recipients. Moreover, seven relapses and 31 deaths occurred among the remaining nonrandomized patients. Thus, treatment failed in approximately one-third of the patients (63 of 194).

Multifactorial analysis of a number of pretreatment variables in the 194 patients showed that certain factors significantly correlated with a favorable outcome: headache as a presenting symptom (P = .005), normal mental status (P = .0001), and a CSF white cell count of >20/mm^3 (P = .04). By contrast, univariate analysis of pretreatment variables indicated that other factors may be predictive of a poor outcome: presence of one or more underlying diseases (including hematopoietic disorders and AIDS; P = .04), corticosteroid or immunosuppressive therapy (P = .05), pretreatment cryptococcal antigen titers of ≥1:32 in serum (P = .05), and posttreatment antigen titers of ≥1:8 in serum (P = .01) or CSF (P = .06).

In light of these results, it was the authors' recommendation that the 4-week regimen be reserved for the specific subset of low-risk patients, defined according to the above criteria. To date, however, the suggested prognostic categories and criteria have not been tested prospectively.

The incidence of toxic effects attributable to either amphotericin B or flucytosine was similar for the two treatment regimens. Among the 91 randomized patients, 44% of those in the 4-week group and 43% of those in the 6-week group had some type of adverse reaction. Among all 194 patients studied, 103 (53%) had one or more major adverse reactions; two deaths were related to amphotericin B–induced azotemia, and three deaths were attributable (at least partly) to flucytosine toxicity.

Thus, the toxicity and success rate associated with these amphotericin B/flucytosine regimens remain unsatisfactory. In light of the results of this clinical trial, perhaps longer—rather than shorter—periods of treatment should be evaluated.

Advances in Antimycotic Therapy: The Azoles

Given the clinical experience with amphotericin B and flucytosine, there is clearly a need for a more consistently effective and nontoxic regimen for the treatment of cryptococcal meningitis [30, 31]. Thus, interest in new antifungal compounds has remained

Table 2. Risk groups proposed on the basis of prognostic factors.

Pretreatment mental status	Headache as a presenting symptom	Pretreatment CSF white cell count (no./mm^3)	No. of patients	1-year mean estimated "cure" rate ±SE (%)	Proposed risk group
Normal	Yes	20	16	93 ± 6	Low
Normal	Yes	20	53	88 ± 5	Low
Lethargy	Yes	20	28	85 ± 7	Low
Normal	No	20	14	69 ± 13	High
Lethargy	No	20	10	50 ± 16	High
Lethargy	Yes	20	13	47 ± 16	High
Obtundation, stupor, or coma	No	20	9	53 ± 18	High
Normal	No	20	13	33 ± 18	High
Obtundation, stupor, or coma	No	20	3	33 ± 29	High
Lethargy	No	20	9	27 ± 17	High
Obtundation, stupor, or coma	Yes	20	16	17 ± 18	High
Obtundation, stupor, or coma	Yes	20	2	0	High

NOTE. Table is reprinted with permission from the *New England Journal of Medicine* [7]. A total of 186 patients had all three pretreatment factors recorded. Risk was determined by the Kaplan-Meier method. The estimated overall "cure" rate for the low-risk group was 88% ± 3%; for the high-risk group, it was 38% ± 7%.

high. One group of drugs that has exhibited considerable promise is the antifungal azoles.

Structure and Mechanism of Action

The basic structural unit of all azoles is a five-member azole ring. Figure 1 illustrates the structures of five azole compounds. The imidazoles (i.e., clotrimazole, miconazole, ketoconazole) contain two nitrogen atoms in the azole ring, whereas the triazoles (fluconazole, itraconazole) contain three. Although these agents may exert several adverse effects on fungi, their primary mode of action is inhibition of ergosterol biosynthesis in the fungal cell membrane [32] secondary to inhibition of cytochrome P450 enzyme activity, which is necessary for the demethylation of 14-α-methylsterols to ergosterol. The following discussion focuses on the major pharmacologic and clinical features of the azoles.

The Imidazoles

Clotrimazole and miconazole. Early studies showed that oral clotrimazole was characterized by low activity, high toxicity, and rapid degradation by liver enzymes [33], whereas miconazole was distinguished by a short half-life and a variety of serious toxicities and had to be administered intravenously [33]. Although miconazole can be injected intrathecally, its efficacy in treating cryptococcal meningitis has not been established.

Ketoconazole. The introduction of ketoconazole in the late 1970s marked a significant advance in antifungal therapy, since it was the first broad-spectrum antifungal that could be given by the oral route. Ketoconazole is available in tablet form for oral administration. Absorption can be erratic, but satisfactory serum concentrations are usually obtained when gastric acidity is normal. However, ketoconazole does not readily diffuse into CSF. Although high-dose ketoconazole (800–2,000 mg) can produce low CSF levels in experimental therapy for coccidioidal meningitis, such a dosage is poorly tolerated, is not approved by the U.S. Food and Drug Administration, and therefore cannot be recommended for cryptococcal meningitis [34–43].

Ketoconazole also appears to interact significantly with at least two other important drugs, rifampin [44] and cyclosporine, in a manner that leads to increased levels [45]. Given the high incidence of cryptococcal meningitis in immunocompromised patients, the latter interaction is of particular concern. As mentioned above, the absorption of ketoconazole can be erratic, secondary to problems with maintaining a low gastric pH [46, 47]. This problem is particularly apparent in AIDS patients. Consequently, ketoconazole must not be administered concomitantly with antacids or H_2 blockers, such as

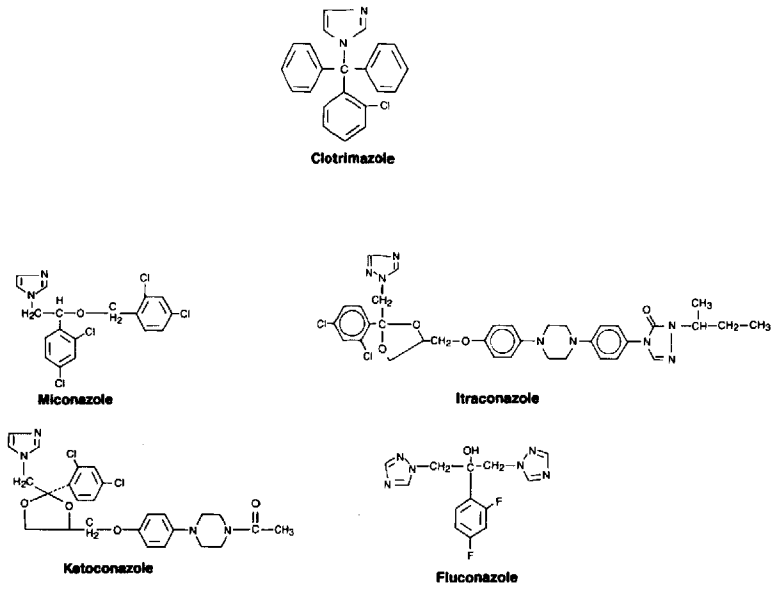

Figure 1. Structures of representative antifungal azole compounds.

cimetidine. Determination of serum concentrations of ketoconazole should be considered when a patient fails to respond to the usual doses.

The Triazoles

The results of recent studies suggest that two new oral triazoles, fluconazole and itraconazole, may be particularly well suited to the treatment of cryptococcal meningitis. At present, these are the only two investigational triazoles to have been studied extensively in vitro and in animal models as well as in limited clinical trials. A third oral azole compound, SCH 39304, is in the early stages of development [48–50]. Table 3 compares the major features of fluconazole and itraconazole with those of ketoconazole.

Pharmacokinetic characteristics. In terms of pharmacokinetics, ketoconazole, fluconazole, and itraconazole differ markedly from one another. Fluconazole has a lower molecular weight than either of the other azoles and is more water soluble. It is minimally protein bound (11% vs. > 90% for each of the other drugs) and has high relative bioavailability (90% vs. 75% for ketoconazole and 85% for itraconazole). The absorption of both ketoconazole and itraconazole is affected by ingestion with a meal (the peak level being delayed); the absorption of fluconazole is the same whether the drug is taken with food or in a fasting state.

Table 3. Comparison of the major characteristics of three azole compounds.

Characteristic	Compound		
	Keto-conazole	Itra-conazole	Flu-conazole
Route of administration	po	po	po/iv
Water solubility (pH 7)	Low	Low	High
Cimetidine-antacid effect	+++	+++	–
Half-life (h)	0	17	26
Protein-binding (%)	>90	>90	11
CSF serum levels (μg/mL)	~0.05	~0.05	>0.60
Urine levels	No	No	Yes
Testosterone/cortisol suppression	++	–	–
Relative potency against *Candida*			
In vitro	1	1	1/16
In vivo	1	4–8	20
Activity against *Aspergillus*	–	++	++(?)
Activity against *Cryptococcus*	±	++	+++

NOTE. Abbreviations and symbols: po = oral; iv = intravenous; – = none; + = minimal; ++ = moderate; +++ = marked.

Ketoconazole and itraconazole are extensively degraded in the liver to inactive metabolites, which are excreted via both bile and urine. Fluconazole, in contrast, is excreted primarily in the urine, mainly as unchanged active drug. The volume of distribution of both fluconazole and itraconazole is greater than that of ketoconazole. In addition, both fluconazole and itraconazole have prolonged half-lives (26 hours and 17 hours, respectively) as compared with ketoconazole (2–8 hours).

Fluconazole. One of the distinguishing pharmacokinetic characteristics of fluconazole is its high degree of penetration into the CSF and other body compartments. Several studies in animal models of cryptococcal meningitis (including models in subhuman primates) have demonstrated that the concentrations of fluconazole in the CSF are ~60%–80% of serum concentrations in the presence of both uninflamed and inflamed meninges [51–55].

Findings in humans have been similar. A recent long-term pharmacokinetic evaluation of fluconazole in patients with coccidioidal meningitis demonstrated that the mean ratio of the concentration of fluconazole in CSF to that in serum was 74% after a dosage of 50 mg/d and 89% after a dosage of 100 mg/d [54]. Another report involving patients with a variety of serious mycoses cited a mean CSF-to-serum concentration ratio of 0.89 [55]. In a study of AIDS patients with various forms of cryptococcosis, the CSF-to-serum concentration ratios ranged from 0.25 to 0.88 after at least 1 week of treatment with fluconazole (100 mg/d) [56].

The extensive CSF penetration of fluconazole may be due in part to its high water solubility and its low protein binding in plasma; both characteristics leave the majority of drug available for distribution throughout the body. Fluconazole has been shown to penetrate into all body tissues, including the CNS and peritoneum [57].

Itraconazole. Itraconazole shares many of the pharmacokinetic properties of ketoconazole, including high lipophilicity, good absorption after oral administration, a high degree of protein binding, and extensive distribution in tissues (table 3). Although itraconazole tends to concentrate in cells and phagocytes, the ratio of tissue to plasma levels suggests a

high affinity of the drug for tissues usually infected with fungi. As noted previously, the serum half-life of itraconazole is considerably longer than that of ketoconazole. Tests have shown that oral itraconazole is five times more active than oral ketoconazole in vivo against *Paracoccidioides brasiliensis* [58] and 100 times more inhibitory in vitro against *Aspergillus fumigatus* and *Aspergillus niger* [59].

Despite its relatively poor penetration into CSF, itraconazole appears to be effective for the treatment of cryptococcal meningitis [60, 60a]. Results of studies in animal models have indicated that itraconazole shows more promise in this regard than does ketoconazole [52, 60]. This finding confirms that high CSF drug concentrations, per se, are not mandatory. Amphotericin B illustrates this apparent paradox for successful treatment of cryptococcal infections. Perhaps itraconazole reaches high concentrations in the brain but, because of its lipophilicity, is found at extremely low concentrations in the CSF [61].

A recent report described the use of itraconazole (200 mg/d) in three AIDS patients with cryptococcal meningitis in whom conventional antifungal therapy had been terminated because of intolerance or toxicity (two cases) and inefficacy of the highest administrable dose of amphotericin B (one case) [62]. One month after the initiation of itraconazole therapy, clinical symptoms had been suppressed in two of the patients and additional clinical improvement was noted in the third patient. CSF cultures were negative in all three cases. In preliminary studies in another group of 16 AIDS patients, cryptococcal meningitis was treated with 100–200 mg of itraconazole daily. Seven of the patients who received ≥2 months of therapy experienced marked improvement or cure [63].

Both itraconazole and fluconazole appear to be better tolerated than ketoconazole, and both produce a lower incidence of gastrointestinal side effects and elevations in hepatic enzymes. Furthermore, the inhibition of adrenal or testicular steroidogenesis seen with ketoconazole has not yet been observed with either itraconazole or fluconazole.

Treatment of Cryptococcal Meningitis in Patients with AIDS

Cryptococcal meningitis is an important cause of CNS disease in AIDS patients. Among the infectious agents causing neurologic disease in this population, *C. neoformans* ranks third in frequency after the human immunodeficiency virus (HIV) and *Toxoplasma gondii* [64, 65], infecting up to 10% of patients [66]. The clinical presentation of cryptococcal meningitis in AIDS patients is nonspecific and is often associated with an absence of inflammation and with unusually high serum titers of cryptococcal antigen (up to 1:1,000,000) [67].

The goals of treatment in AIDS patients with cryptococcal meningitis also differ markedly from those of therapy in their immunocompetent counterparts. Instead of cure, the primary objectives are to improve the patient's quality of life, minimize the encumbrance of prolonged drug therapy, and suppress relapses after initial intensive primary treatment.

While combination therapy with amphotericin B and flucytosine has substantially improved outcome in AIDS patients with cryptococcal meningitis, the failure rate among immunocompromised patients is considerably higher than that among immunocompetent patients [68–70]. In addition, the relatively high toxicity of flucytosine in patients with AIDS may limit its use [70]. Thus, attention has recently been focused on the use of the new triazoles in the treatment of cryptococcal meningitis in patients with AIDS.

In 1987 and 1988, the first two cures of cryptococcal meningitis in AIDS patients treated with fluconazole were reported [71, 72]. Several recently completed studies suggest that fluconazole represents an important advance in the long-term treatment of AIDS patients with cryptococcal meningitis. In the first of these open-label studies [61], 22 AIDS patients with infections caused by *C. neoformans* were treated with 50–400 mg of fluconazole daily for up to 64 weeks. Seven of the patients had active, culture-positive infections (five of which were meningitis); 15 had undergone successful treatment with amphotericin B and were receiving fluconazole as prophylaxis against relapse. Of the seven patients with active cryptococcal infection, four had a favorable clinical and microbiologic response to fluconazole. The drug sterilized the CSF of two previously untreated patients with active infection as well as that of two patients in whom treatment with amphotericin B had failed. Prophylaxis with fluconazole prevented relapse for periods ranging from 11 to 64 weeks in 14 of the 15 patients successfully treated with amphotericin B. Adverse reactions in this popu-

lation were generally mild and transient, consisting primarily of an increase in hepatic enzymes (four patients).

A second open-label study of fluconazole was conducted in 20 AIDS patients, 19 of whom had cryptococcal meningitis [73]. Patients were treated with amphotericin B for 20–257 days before beginning treatment with fluconazole (50–200 mg/d); eight patients had received flucytosine in combination with amphotericin B. Of the evaluatable patients, nine (47%) of 19 were successfully maintained on fluconazole for 9–21 months (median, 11 months). The CSF cultures of these patients were consistently negative. Two patients relapsed during treatment; one had a positive and the other a negative CSF culture. Reinstitution of amphotericin B therapy produced improvement in both cases. Of the five patients who died during fluconazole treatment, none had clinical or laboratory features suggestive of cryptococcal meningitis. An additional two patients died following discontinuation of fluconazole therapy; in both cases, postmortem brain cultures were sterile. Fluconazole was well tolerated during this prolonged period of administration; the most common adverse reaction—nausea—did not lead to discontinuation of therapy in any case.

Thirty-five AIDS patients with cryptococcal meningitis participated in a third open-label multicenter study in which fluconazole was administered as initial therapy (unpublished data). After an initial loading dose of 400 mg, patients were assigned to receive 45–60 days of treatment with either 150–200 mg/d or 400 mg/d. Once CSF cultures became negative, patients were maintained on 100–200 mg of fluconazole daily for the remainder of the study.

By day 60 of treatment, 26 (89.6%) of the 29 evaluatable patients were asymptomatic or had improved. Improvement was rapid (within 3–5 days) and frequently dramatic, and clinical resolution was obtained by week 3 or 4. Of the three patients who died, only one had progressive cryptococcosis. The mycologic results clearly favored the higher-dose regimen. Eleven of 13 patients given 400 mg/d had negative CSF cultures on days 45–60, as compared with seven of 13 patients given 150–200 mg/d (table 4). Three of the 18 patients with negative CSF cultures who continued to receive maintenance therapy relapsed: one on day 20, one on day 68, and one on day 150.

Fluconazole was well tolerated; there were no cases in which therapy had to be discontinued because of adverse effects. Virtually all clinical and biologic signs and symptoms observed during the course of therapy were related to the patients' immunocompromised state.

Table 4. Results of microbiologic study of CSF in 29 AIDS patients whose cryptococcal meningitis was treated with fluconazole.

Study or event	Result* in patients given indicated dosage (day 30, day 45–60)	
	150–200 mg/d (n = 16)	400 mg/d (n = 13)
Positive india ink test	8/15, 6/13	5/13, 2/13
Positive culture	7/15, 6/13	7/13, 2/13
Death	1/16, 3/16	0/13, 0/13

NOTE. Table is adapted from [72].

* Number with indicated result/total number assessed.

The majority of clinical studies of fluconazole in patients with cryptococcal meningitis have been conducted in AIDS patients. However, the results of studies conducted in patients without AIDS suggest that fluconazole is effective and well tolerated. One investigation of 15 patients with cryptococcal meningitis revealed sterilization of CSF in 11 of 15 cases [74]. In another study, eight non-AIDS patients (age range, 32–71 years; median age, 45 years) had chronic coccidioidal meningitis (>1 year in duration) that had not responded to conventional therapy. Five of these patients responded to fluconazole therapy, and three could not be evaluated. At dosages of 50 and 100 mg/d, the mean ratio of the concentration in CSF to that in plasma was 74% and 89%, respectively. Fluconazole demonstrated a prolonged half-life at both doses in both CSF and plasma. Toxicity was limited [54].

Overall, accumulated experience with more than 2,000 patients or volunteers treated with dosages of fluconazole ranging from 50 to 200 mg/d for up to 64 weeks has shown that the drug is well tolerated, with minor adverse effects reported in <5% of patients [75]. Although three cases of Stevens-Johnson syndrome in patients receiving fluconazole have been reported worldwide, the association of the drug with this entity has not been definitively established.

As a result of the favorable pharmacologic, preclinical, and clinical findings of fluconazole in the treatment of cryptococcal meningitis, two prospective, randomized clinical studies have been ini-

tiated by the Mycoses Study Group and the AIDS Clinical Trials Units of the National Institute of Allergy and Infectious Diseases; one study is comparing fluconazole (200 mg/d) with conventional therapy in patients with acute cryptococcal meningitis (mainly those with AIDS), and the other is comparing fluconazole (200 mg/d) with amphotericin B (1.0 mg/[kg·w]) as prophylaxis for cryptococcal meningitis in AIDS patients whose cultures are negative following primary therapy.

Conclusions

This article reviews the past 30 years of clinical experience with the drug treatment of cryptococcal meningitis. While amphotericin B and flucytosine remain widely used for this purpose, problems with potential toxicity and less-than-optimal efficacy have spurred the development of alternative therapies that offer considerable clinical promise.

The antifungal triazoles (fluconazole, itraconazole, SCH 39304) appear to combine many desirable pharmacokinetic and pharmacodynamic characteristics. The promising results of studies in animals warrant intensive investigation of clinical utility of these agents in the treatment of cryptococcal meningitis.

Of the investigational triazoles, fluconazole has been used most in the treatment of patients with cryptococcal meningitis. The results of three recently completed studies of AIDS patients with cryptococcal meningitis suggest that fluconazole may offer an advantage over existing therapies in this particularly challenging situation. Experiences with itraconazole in a limited number of patients with cryptococcosis are also highly encouraging.

References

1. Meunier-Carpentier F, Kiehn TE, Armstrong D. Fungemia in the immunocompromised host: changing patterns, antigenemia, high mortality. Am J Med **1981**;71:363–70
2. Schwartz RS, Mackintosh FR, Schrier SL, Greenberg PL. Multivariate analysis of factors associated with invasive fungal disease during remission induction therapy for acute myelogenous leukemia. Cancer **1984**;53:411–9
3. Butler WT, Alling DW, Spickard A, Utz JP. Diagnostic and prognostic value of clinical and laboratory findings in cryptococcal meningitis: a follow-up study of forty patients. N Engl J Med **1964**;270:59–67
4. McCullough NB, Louria DB, Hilbish TF, Thomas LB, Emmons C. Cryptococcosis: clinical staff conference at the National Institutes of Health. Ann Intern Med **1958**;49: 642–61
5. Spickard A, Butler WT, Andriole V, Utz JP. The improved prognosis of cryptococcal meningitis with amphotericin B therapy. Ann Intern Med **1963**;58:66–83
6. Sarosi GA, Parker JD, Doto IL, Tosh FE. Amphotericin B in cryptococcal meningitis: long-term results of treatment. Ann Intern Med **1969**;71:1079–87
7. Dismukes WE, Cloud G, Gallis HA, Kerkering TM, Medoff G, Craven PC, Kaplowitz LG, Fisher JF, Gregg CR, Bowles CA, Shadomy S, Stamm AM, Diasio RB, Kaufman L, Soong S-J, Blackwelder WC, and the National Institute of Allergy and Infectious Diseases Mycoses Study Group. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. N Engl J Med **1987**;317:334–41
8. Kotler-Brajtburg J, Price HD, Medoff G, Schlessinger D, Kobayashi GS. Molecular basis for the selective toxicity of amphotericin B for yeast and filipin for animal cells. Antimicrob Agents Chemother **1974**;5:377–82
9. Kotler-Brajtburg J, Medoff G, Kobayashi GS, Schlessinger D, Atallah A. Sensitivity to amphotericin B and the cholesterol: phospholipid molar ratios of 3T3, L, BHK and HeLa cells. Biochem Pharmacol **1977**;26:705–10
10. Little JR, Blanke TJ, Valeriote F, Medoff G. Immunoadjuvant and antitumor properties of amphotericin B. In: Chirigos MA, ed. Immune modulation and control of neoplasia by adjuvant therapy. New York: Raven Press, **1978**: 381–7
11. Shirley SF, Little JR. Immunopotentiating effect of amphotericin B. I. Enhanced contact sensitivity in mice. J Immunol **1979**;123:2878–82
12. Shirley SF, Little JR. Immunopotentiating effects of amphotericin B. II. Enhanced in vitro proliferative responses of murine lymphocytes. J Immunol **1979**;123:2883–9
13. Butler WT, Bennett JE, Alling DW, Wertlake PT, Utz JP, Hill GJ III. Nephrotoxicity of amphotericin B: early and late effects in 81 patients. Ann Intern Med **1964**;61:175–87
14. Utz JP, moderator. Amphotericin B toxicity. Ann Intern Med **1964**;61:334–54
15. Medoff G, Kobayashi GS. Strategies in the treatment of systemic fungal infections. N Engl J Med **1980**;302:145–55
16. Polak A, Scholer HJ. Mode of action of 5-fluorocytosine and mechanisms of resistance. Chemotherapy **1975**;21: 113–30
17. Shadomy S, Shadomy HJ, Utz JP. In vivo susceptibility of *Cryptococcus neoformans* to hamycin, amphotericin B, and 5-fluorocytosine. Infect Immun **1970**;1:128–34
18. Block ER, Bennett JE. The combined effect of 5-fluorocytosine and amphotericin B in the therapy of murine cryptococcosis. Proc Soc Exp Biol Med **1973**;142: 476–80
19. Hamilton JD, Elliott DM. Combined activity of amphotericin B and 5-fluorocytosine against *Cryptococcus neoformans* in vitro and in vivo in mice. J Infect Dis **1975**; 131:129–37
20. Steer PL, Marks MI, Klite PD, Eickhoff TC. 5-Fluorocytosine: an oral antifungal compound: a report on clinical and laboratory experience. Ann Intern Med **1972**;76:15–22
21. Kauffman CA, Carleton JA, Frame PT. Simple assay for 5-fluorocytosine in the presence of amphotericin B. Antimicrob Agents Chemother **1976**;9:381–3
22. Kauffman CA, Frame PT. Bone marrow toxicity associated with 5-fluorocytosine therapy. Antimicrob Agents Chemother **1977**;11:244–7

23. Diasio RB, Lakings DE, Bennett JE. Evidence for conversion of 5-fluorocytosine to 5-fluorouracil in humans: possible factor in 5-fluorocytosine clinical toxicity. Antimicrob Agents Chemother **1978**;14:903–8
24. Scholer HJ. Grundlagen und Ergebnisse der antimykotischen Chemotherapie mit 5-fluorocytosin. Chemotherapy **1976**; 22(Suppl 1):103–46
25. Block ER, Jennings AE, Bennett JE. 5-Fluorocytosine resistance in *Cryptococcus neoformans*. Antimicrob Agents Chemother **1973**;3:649–56
26. Medoff G, Comfort M, Kobayashi GS. Synergistic action of amphotericin B and 5-fluorocytosine against yeast-like organisms. Proc Soc Exp Biol Med **1971**;138:571–4
27. Kwan CN, Medoff G, Kobayashi GS, Schlessinger D, Raskas HJ. Potentiation of the antifungal effects of antibiotics by amphotericin B. Antimicrob Agents Chemother **1972**; 2:61–5
28. Utz JP, Garriques IL, Sande MA, Warner JF, Mandell GL, McGehee RF, Duma RJ, Shadomy S. Therapy of cryptococcosis with a combination of flucytosine and amphotericin B. J Infect Dis **1975**;132:368–73
29. Bennett JE, Dismukes WE, Duma RJ, Medoff G, Sande MA, Gallis H, Leonard J, Fields BT, Bradshaw M, Haywood H, McGee ZA, Cate TR, Cobbs CG, Warner JF, Alling DW. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. N Engl J Med **1979**;301:126–31
30. De Wytt CN, Dickson PL, Holt GW. Cryptococcal meningitis: a review of 32 years experience. J Neurol Sci **1982**; 53:283–92
31. Sabetta JR, Andriole VT. Cryptococcal infection of the central nervous system. Med Clin North Am **1985**;69(2):333–44
32. Alsip SG, Stamm AM, Dismukes WE. Ketoconazole, miconazole, and other imidazoles. In: Sarosi GA, Davies SF, eds. Fungal diseases of the lung. Orlando: Grune and Stratton, **1986**:335–76
33. Plempel M. Pharmacokinetics of imidazole antimycotics. Postgrad Med J **1979**;55:662–6
34. Heiberg JK, Svejgaard E. Toxic hepatitis during ketoconazole treatment. Br Med J **1981**;283:825–6
35. Janssen PAJ, Symoens JE. Hepatic reactions during ketoconazole treatment. Am J Med **1983**;74(Suppl 1B):80–5
36. Lewis JH, Zimmerman HJ, Benson GD, Ishak KG. Hepatic injury associated with ketoconazole therapy: analysis of 33 cases. Gastroenterology **1984**;86:503–13
37. DeFelice R, Johnson DG, Galgiani JN. Gynecomastia with ketoconazole. Antimicrob Agents Chemother **1981**;19: 1073–4
38. Pont A, Williams PL, Azhar S, Reitz RE, Bochra C, Smith ER, Stevens DA. Ketoconazole blocks testosterone synthesis. Arch Intern Med **1982**;142:2137–40
39. Pont A, Graybill JR, Craven PC, Galgiani JN, Dismukes WE, Reitz RE, Stevens DA. High-dose ketoconazole therapy and adrenal and testicular function in humans. Arch Intern Med **1984**;144:2150–3
40. Pont A, Williams PL, Loose DS, Feldman D, Reitz RE, Bochra C, Stevens DA. Ketoconazole blocks adrenal steroid synthesis. Ann Intern Med **1982**;97:370–2
41. Klatt EC, Shibata D. Cytomegalovirus infection in the acquired immunodeficiency syndrome: clinical and autopsy findings. Arch Pathol Lab Med **1988**;112:540–4
42. Greene LW, Cole W, Greene JB, Levy B, Louie E, Raphael B, Waitkevicz J, Blum M. Adrenal insufficiency as a complication of the acquired immunodeficiency syndrome. Ann Intern Med **1984**;101:497–8
43. Sugar AM, Alsip SG, Galgiani JN, Graybill JR, Dismukes WE, Cloud GA, Craven PC, Stevens DA. Pharmacology and toxicity of high-dose ketoconazole. Antimicrob Agents Chemother **1987**;31:1874–8
44. Engelhard D, Stutman HR, Marks MI. Interaction of ketoconazole with rifampin and isoniazid. N Engl J Med **1984**;311:1681–3
45. Dieperink H, Moller J. Ketoconazole and cyclosporin [letter]. Lancet **1982**;2:1217
46. Lake-Bakaar G, Quadros E, Beidas S, Elsakr M, Tom W, Wilson DE, Dincsoy HP, Cohen P, Straus EW. Gastric secretory failure in patients with the acquired immunodeficiency syndrome (AIDS). Ann Intern Med **1988**;109:502–4
47. Lake-Bakaar G, Tom W, Lake-Bakaar D, Gupta N, Beidas S, Elsakr M, Straus E. Gastropathy and ketoconazole malabsorption in the acquired immunodeficiency syndrome (AIDS). Ann Intern Med **1988**;109:471–3
48. Restrepo BI, Ahrens J, Graybill JR. Efficacy of Sch 39304 (SCH) in murine cryptococcosis [abstract no. 170]. In: Program and abstracts of the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1988**:140
49. Lin C, Kim H, Lapiguera A, Loebenberg D, Miller GH, Symchowicz S. Comparative pharmacokinetics of Sch 39304 and fluconazole in mice, rabbits, S. monkeys and C. monkeys [abstract no. 163]. In: Program and abstracts of the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1988**:138
50. Kramer W, Kim H, Symchowicz S, Perentesis G, Affrime M, Lin C. Pharmacokinetics of Sch 39304 in man [abstract no. 165]. In: Program and abstracts of the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1988**:139
51. Perfect JR, Durack DT. Penetration of imidazoles and triazoles into cerebrospinal fluid of rabbits. J Antimicrob Chemother **1985**;16:81–6
52. Perfect JR, Savani DV, Durack DT. Comparison of itraconazole and fluconazole in treatment of cryptococcal meningitis and candida pyelonephritis in rabbits. Antimicrob Agents Chemother **1986**;29:579–83
53. Arndt CAS, Walsh TJ, McCully CL, Balis FM, Pizzo PA, Poplack DG. Fluconazole penetration into cerebrospinal fluid: implications for treating fungal infections of the central nervous system. J Infect Dis **1988**;157:178–80
54. Tucker RM, Williams PL, Arathoon EG, Levine BE, Hartstein AI, Hanson LH, Stevens DA. Pharmacokinetics of fluconazole in cerebrospinal fluid and serum in human coccidioidal meningitis. Antimicrob Agents Chemother **1988**;32:369–73
55. Rinaldi MG, Robinson PA, Graybill JR, Stern JJ, Sugar AM, Hartman BJ, Hilligoss DM. Fluconazole (FLU) concentrations in patients undergoing antifungal therapy [abstract 66]. In: Program and abstracts of the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1988**:121
56. Stern JJ, Hartman BJ, Sharkey P, Rowland V, Squires KE,

Murray HW, Graybill JR. Oral fluconazole therapy for patients with acquired immunodeficiency syndrome and cryptococcosis: experience with 22 patients. Am J Med **1988**;85:477–80

57. Humphrey MJ, Jevons S, Tarbit MH. Pharmacokinetic evaluation of UK-49,858, a metabolically stable triazole antifungal drug, in animals and humans. Antimicrob Agents Chemother **1985**;28:648–53
58. Negroni R, Finquelievich JL, Gosis AS. Estudio comparativo de la eficacia del itraconazol y el ketoconazol en el tratamiento de la paracoccidioidomicosis experimental. Med Cutan Ibero Lat Am **1987**;15:455–60
59. Marichal P, Gorrens J, Vanden Bossche H. The action of itraconazole and ketoconazole on growth and sterol synthesis of *Aspergillus fumigatus* and *Aspergillus niger*. Sabouraudia **1985**;23:13–21
60. Graybill JR, Ahrens JR. R51211 (itraconazole) therapy of murine cryptococcosis. Sabouraudia **1984**;22:445–53

60a. Denning DW, Tucker RM, Hanson LH, Hamilton JR, Stevens DA. Itraconazole therapy for cryptococcal meningitis and cryptococcosis. Arch Intern Med **1989**;149:2301

61. Brochure on basic medical information on itraconazole. Piscataway, NJ: Janssen Pharmaceuticals, **1987**
62. Viviani MA, Tortorano AM, Giani PC, Arici C, Goglio A, Crocchiolo P, Almaviva M. Itraconazole for cryptococcal infection in the acquired immunodeficiency syndrome [letter]. Ann Intern Med **1987**;106:166
63. Cauwenbergh G. Traitement par de cryptococcose cérébral et pulmonaire. Le Bulletin de la Société Française de Mycologie Médicale **1988**;17:121–6
64. Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience of UCSF and review of the literature. J Neurosurg **1985**;62:475–95
65. Gabuzda DH, Hirsch MS. Neurologic manifestations of infection with human immunodeficiency virus. Clinical features and pathogenesis. Ann Intern Med **1987**;107:383–91
66. Armstrong D, Gold JWM, Dryjanski J, Whimbey E, Polsky B, Hawkins C, Brown AE, Bernard E, Kiehn TE. Treatment of infections in patients with the acquired immunodeficiency syndrome. Ann Intern Med **1985**;103:738–43
67. Eng RHK, Bishburg E, Smith SM, Kapila R. Cryptococcal infections in patients with acquired immune deficiency syndrome. Am J Med **1986**;81:19–23
68. Diamond RD, Bennett JE. Prognostic factors in cryptococcal meningitis: a study in 111 cases. Ann Intern Med **1974**;80:176–81
69. Kaplan MH, Rosen PP, Armstrong D. Cryptococcosis in a cancer hospital: clinical and pathological correlates in forty-six patients. Cancer **1977**;39:2265–74
70. Kovacs JA, Kovacs AA, Polis M, Wright WC, Gill VJ, Tuazon CU, Gelmann EP, Lane HC, Longfield R, Overturf G, Macher AM, Fauci AS, Parrillo JE, Bennett JE, Masur H. Cryptococcosis in the acquired immunodeficiency syndrome. Ann Intern Med **1985**;103:533–8
71. Byrne WR, Wajszczuk CP. Cryptococcal meningitis in the acquired immunodeficiency syndrome (AIDS): successful treatment with fluconazole after failure of amphotericin B. Ann Intern Med **1988**;108:384–5
72. Dupont B, Drouhet E. Cryptococcal meningitis and fluconazole [letter]. Ann Intern Med **1987**;106:778
73. Sugar AM, Saunders C. Oral fluconazole as suppressive therapy of disseminated cryptococcosis in patients with acquired immunodeficiency syndrome. Am J Med **1988**;85:481–9

74. Data on file. New York: Roerig, **1989**

75. Saag MS, Dismukes WE. Azole antifungal agents: emphasis on new triazoles. Antimicrob Agents Chemother **1988**;32:1–8