Role of Azoles in Antifungal Therapy

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The addition of itraconazole and fluconazole to the antifungal armamentarium has resulted in less toxic, easily administered therapy for both endemic and opportunistic mycoses. Itraconazole has become the treatment of choice for most patients with mild-to-moderate histoplasmosis, blastomycosis, and sporotrichosis. Coccidioidomycosis is effectively treated with either itraconazole or fluconazole; fluconazole has become the drug of choice for the treatment of coccidoidal meningitis. In several large cooperative trials, fluconazole has been shown to have a useful role in the treatment of patients with candidemia, localized forms of mucocutaneous and visceral candidiasis, and cryptococcal meningitis.

The 1960s and 1970s could be considered the amphotericin B era. During those two decades, treatment of the major endemic mycoses usually involved hospitalization for all or a portion of the 6–12 weeks required for administration of amphotericin B. Therapy was associated with significant toxic effects, and many patients were reluctant to undergo this intensive treatment regimen. An important outcome of the multicenter treatment trials that were carried out during those two decades was the firmly established guidelines that were established for therapy for chronic cavitary pulmonary histoplasmosis, progressive disseminated histoplasmosis, and pulmonary and disseminated blastomycosis [1–5]. Opportunistic fungal infections, although documented as a problem, were not nearly as prominent as they were to become a few decades later.

The 1980s could be considered the ketoconazole era. Introduction of this oral imidazole antifungal drug allowed, for the first time, outpatient therapy for several endemic mycoses, notably histoplasmosis, blastomycosis, and coccidioidomycosis. Although less toxic than amphotericin B, ketoconazole proved to be difficult to administer at dosages of ≥800 mg daily because of the frequent occurrence of side effects [6, 7].

Ketoconazole proved efficacious for the treatment of both chronic cavitary pulmonary and disseminated histoplasmosis; the overall response rate among patients treated for at least 6 months was 85% [7]. The response rate among patients with blastomycosis who received ketoconazole treatment for at least 6 months was close to 90% [7, 8]; for these patients, the 800-mg dose was more efficacious than was the 400-mg dose [7]. Although patients with coccidioidomycosis responded less well than did those with histoplasmosis or blastomycosis, the results were comparable with those noted with amphotericin B [9, 10].

However, it should be noted that the Mycoses Study Group trial for the treatment of coccidioidomycosis with ketoconazole excluded patients with life-threatening or severe coccidioidal mycosis.

During this decade, the incidence of opportunistic fungal infections increased as the number of immunosuppressed patients increased. These infections became a major cause of morbidity and mortality in patients receiving transplanted organs, undergoing chemotherapy for hematologic malignancies, and receiving corticosteroid therapy for a variety of illnesses.

The 1990s can be considered the triazole era. This decade has witnessed the move toward outpatient therapy for most endemic mycoses, the establishment of attractive alternatives for the treatment of several forms of sporotrichosis, and the introduction of the least toxic antifungal agents yet developed. Fluconazole and itraconazole were released in 1990 and 1992, respectively, and both agents have found important niches in the treatment of fungal infections.

For the first time, it became possible to treat several different opportunistic fungal infections with oralazole drugs rather than with intravenous amphotericin B. Unfortunately, as safe, efficacious oral drugs became readily available as treatment of fungal infections, resistance to these agents appeared in scattered areas throughout the world. The prevalence of azole-resistant isolates, especially those from patients with AIDS, appears to be increasing; this increase looms as the most significant negative effect of the introduction of azoles during this decade [11–16].

This review focuses on the role of azoles in the treatment of fungal infections. For the endemic mycoses, it is important to note that there are no trials directly comparingazole drugs with amphotericin B. Historical controls have been used with the realization that patient groups and medical practice in the 1980s and 1990s clearly differ from those in the 1960s and 1970s. For several opportunistic fungal infections, namely cryptococcal meningitis and candidemia, a few well-controlled, comparative trials have been performed, and direct comparison of azoles with amphotericin B has helped define the role of azoles in these specific circumstances [17–20].
Itraconazole Treatment of Endemic Mycoses

The benefit of treating blastomycosis with itraconazole has been shown by a Mycoses Study Group trial in which 48 patients were treated with 200–400 mg of itraconazole daily for 6–24 months [21]. The response rate among those patients who received at least 2 months of therapy was 95% (38 of 40 patients), and the overall response rate was 90% (43 of 48 patients). Only one of the 38 patients who had resolution of blastomycosis later relapsed after treatment was stopped. Even though the total number of patients was small, the results were clear-cut; as a result, itraconazole has become the drug of choice for the treatment of blastomycosis. It is important to note that patients with HIV infection, meningeal blastomycosis, and life-threatening infection were excluded from this study; in fact, therapeutic experience with any azole has been limited for patients with these conditions.

Most patients with blastomycosis begin to show a clinical response to itraconazole treatment within the first month; cutaneous lesions and pulmonary infiltrates in most patients start to resolve by 2 months but may take ≥6 months to completely disappear. Although the aforementioned study did not assess duration of therapy, the usual recommendation is at least 6 months or at least 3 months past the time when all lesions have resolved.

Patients with histoplasmosis respond well to itraconazole therapy. Thirty-seven patients with histoplasmosis were enrolled in a Mycoses Study Group trial of 200–400 mg of itraconazole daily for 6–24 months as treatment of chronic cavitary and other forms of pulmonary histoplasmosis and disseminated histoplasmosis [21]. The response rate among patients treated for at least 2 months was 86%, and the overall response rate was 81%. The response rate among 10 patients with disseminated histoplasmosis and seven patients with nodular pulmonary or mediastinal histoplasmosis was 100%, but it was only 65% among the 20 patients with chronic cavitary pulmonary histoplasmosis. These response rates are similar to those associated with ketoconazole and amphotericin B [1–3, 7]. All patients who had persistence of infection or who relapsed were those with chronic cavitary pulmonary histoplasmosis.

Most patients with histoplasmosis should be treated for at least 6 months or for 3 months after all signs of infection have cleared. Those patients who have chronic cavitary pulmonary histoplasmosis generally require therapy for at least 1 year and often longer. In this form of histoplasmosis, the endpoints are blurred because the severe underlying pulmonary disease present in most patients obscures roentgenographically evident improvement and influences the patient’s functional state. Therapy also should be given for at least 1 year or more to those patients with chronic progressive disseminated histoplasmosis.

Histoplasmosis is an AIDS-defining illness; as might be expected, infection in the HIV-positive individual is associated with a worse prognosis than is infection in healthy individuals [22–24]. The disease may be acquired from the environment as a new infection or may be due to reactivation of prior infection with *Histoplasma capsulatum*. In HIV-infected persons, the disease almost always presents as disseminated infection.

In two open-label, noncomparative trials [25, 26], itraconazole was shown to be effective for both primary and maintenance therapy. Wheat et al. [25] found a response rate of 85% among patients with mild-to-moderate histoplasmosis who were treated with 200 mg of itraconazole twice daily. A related study [26] showed that 93% of patients remained relapse free when 200 mg of itraconazole was given twice daily following induction treatment with amphotericin B (total dose, ≥15 mg/kg). Thus, the current standard of practice is to continue itraconazole therapy indefinitely for HIV-infected patients with histoplasmosis. It is important to ascertain that the patient has adequate serum levels of itraconazole since decreased absorption of itraconazole has been noted in HIV-infected patients [27].

The azoles have markedly changed the approach to the treatment of coccidioidomycosis. Both itraconazole and fluconazole appear to be effective therapy for coccidioidomycosis [28–31]. However, the response rates associated with either azole as treatment of coccidioidomycosis are lower than those associated with either azole as treatment of blastomycosis and histoplasmosis. In a recent Mycoses Study Group trial [29], 57% of patients responded to therapy with 400 mg of itraconazole daily. This rate is similar to the response rate noted by other investigators [28] and to that associated with fluconazole [30, 31]. The response rates associated with itraconazole and fluconazole are better than those associated with ketoconazole, but more rigorous criteria for improvement were used in the studies with ketoconazole [9, 10, 32].

Patients with chronic coccidioidomycosis can be treated with any one of the three oral azoles at a dosage of 400 mg daily. Which drug should be used depends on patient tolerance, drug interactions, and cost [32]. If the patient does not respond to 400 mg of ketoconazole, the dose can be raised, but side effects are very common at daily doses of ≥800 mg. Therapy is continued for at least 1 year and often for 2 years. A current Mycoses Study Group trial is comparing itraconazole with fluconazole as treatment of coccidioidomycosis. To date, this is the only comparative trial determining the superiority of one azole over another for the treatment of any endemic mycosis.

Although not approved by the Food and Drug Administration (FDA) for the treatment of sporotrichosis, itraconazole has become the drug of choice for the treatment of this infection. Response rates among patients with lymphocutaneous sporotrichosis vary from 90% to 100% [33–35]. Treatment duration is usually from 3 to 6 months, and the dosage is 100–200 mg of itraconazole daily. Treatment of osteoarticular sporotrichosis is more problematic. Response rates of 73% were reported by Sharkey-Mathis et al. [33], and four of five patients described by Winn et al. [36] responded to itraconazole therapy. The dosage should be 200 mg of itraconazole twice daily, and
treatment should continue for at least 1 year; treatment of patients with osteomyelitis may need to extend longer.

For patients with pulmonary sporotrichosis, treatment with either azoles or amphotericin B has been disappointing [33, 37]. Response rates of 30%–50% are common. Most of these patients have underlying chronic obstructive pulmonary disease, and cavitary lesions are commonly noted. Response to treatment is slow, relapses are expected, and some patients may well require lifelong therapy to suppress growth of Sporothrix schenckii. Generally, 200 mg of itraconazole twice daily is the dosage required.

**When Is Amphotericin B Therapy Indicated for Endemic Mycoses?**

All of the above-mentioned studies excluded patients with life-threatening illness. For these patients, amphotericin B remains the treatment of choice because of its intravenous formulation and rapid onset of action. Thus, patients with acute respiratory distress syndrome, sepsis syndrome, or other evidence of overwhelming infection with *H. capsulatum*, *Blastomyces dermatitidis*, or *Coccidioides immitis* should be treated initially with amphotericin B. After stabilization, therapy can usually be switched to itraconazole.

Frequently, histoplasmosis in patients with AIDS presents as overwhelming infection. These patients should receive initial therapy with amphotericin B; following stabilization, itraconazole can be used as further treatment and subsequent maintenance therapy. Similarly, for HIV-infected individuals with coccidioidomycosis, initial therapy with amphotericin B is warranted for severe infection, which can be followed by subsequent therapy with an azole.

**Itraconazole Treatment of Opportunistic Mycoses**

Investigators have less experience using itraconazole for the treatment of opportunistic fungal infections. The FDA has approved this drug as second-line therapy for aspergillosis in patients who are unable to tolerate amphotericin B treatment or for whom this treatment fails. In a multicenter study of 76 patients with aspergillosis [38], the overall success rate at the end of treatment was 39%. Outcome was dependent on the site being treated: patients with pulmonary infection responded better to treatment than did those with nonpulmonary aspergillosis. Response also varied by the type of underlying illness: patients with solid organ transplants responded better to treatment than did those with bone marrow transplants, patients who were neutropenic responded well if the neutropenia resolved, and patients with AIDS had the worst response.

European studies [39, 40] reported response rates of 63% to 70%, but the definitions of infection due to *Aspergillus* species in these studies were not as stringent as those used by Denning et al. [38]. Drawbacks to itraconazole treatment of aspergillosis center mainly on the lack of an intravenous formulation and reliance on absorption of the oral formulation with slow achievement of steady-state levels of drug.

The role of itraconazole in the treatment of other opportunistic infections, such as candidiasis and cryptococcosis, is less well defined. Itraconazole is effective for the treatment of mucocutaneous candidiasis [41, 42]. However, reported experience with itraconazole treatment of other forms of candidiasis is very limited [43]. A major reason that the drug has not been used extensively as therapy for candidemia is the lack of an intravenous formulation or a readily absorbed oral formulation. Because active drug is not detected in the urine, itraconazole should not be used to treat fungal urinary tract infections.

Experience with primary treatment of cryptococcal meningitis with itraconazole is limited [39, 44–46]. Although some investigators have shown response rates similar to those associated with fluconazole [44], not all studies have noted such success [46]. A Mycoses Study Group/AIDS Clinical Trials Group study of 408 patients with AIDS and cryptococcal meningitis has been completed [47, 48]. Itraconazole was compared with fluconazole as consolidation therapy following an initial 2-week period of induction treatment with amphotericin B, with or without flucytosine. Three hundred six patients finished induction treatment and were randomized to either fluconazole or itraconazole therapy for an additional 8 weeks; no significant differences in clinical or microbiological outcome parameters were noted for either group. However, there was a trend toward greater culture negativity for the group receiving fluconazole treatment [48].

Another study comparing itraconazole with fluconazole as maintenance treatment of cryptococcal meningitis in patients with AIDS [49] showed the superiority of fluconazole (94% of fluconazole-treated patients were relapse free compared with 77% of itraconazole-treated patients). Thus, itraconazole should be considered as second-line therapy for patients with cryptococcosis.

**Fluconazole Treatment of Opportunistic Mycoses**

Fluconazole was released in 1990 for the treatment of cryptococcosis and candidiasis. Several large randomized trials have clearly shown the benefits of fluconazole as treatment of acute cryptococcal meningitis and for prevention of relapse of infection in patients with AIDS [17, 18]. Fluconazole was shown to be as efficacious as amphotericin B as primary therapy for cryptococcal meningitis when 200 mg of fluconazole daily was compared with 0.4–0.5 mg of amphotericin B/(kg·d) [17]. However, the success rates associated with both arms of that study were not adequate, possibly because the doses of drugs used were too low.

In addition, it was noted that *Cryptococcus neoformans* cleared significantly more slowly in CSF of patients treated with fluconazole than in CSF of those receiving amphotericin B therapy. In a small study, Larsen et al. [20] found that amphotericin B was superior to fluconazole as treatment of cryptococ-
cal meningitis in patients with AIDS. However, in this study, larger doses of amphotericin B were used, and fluconosine was combined with amphotericin B.

These observations led to the recently completed multicenter study mentioned above, in which an initial 2-week regimen of induction therapy with amphotericin B (0.7 mg/[kg · d]) with or without fluconosine (100 mg/[kg · d]) was given prior to azole use [47, 48]. The outcomes for both groups were superior to those seen in the initial trial [17]; there was a trend toward improved rates of sterilization of CSF among the group receiving fluconosine therapy [47]. Furthermore, data showing the superiority of adding fluconosine to amphotericin B were noted in the trial of azoles as maintenance therapy for cryptococcal meningitis that was discussed above [49].

Thus, cryptococcal meningitis in patients with AIDS should probably be managed initially with induction therapy with amphotericin B and fluconosine until the patient's condition is stabilized; this treatment should be followed by therapy with fluconazole at a dosage of 400 mg daily for ~3 months. Maintenance therapy with fluconazole for prevention of relapse should follow acute therapy; the dosage of fluconazole should be 200 mg daily [18].

Finally, intriguing data from a study by Larsen et al. [50] have shown the benefit of combining fluconosine (150 mg/[kg · d]) with fluconazole (400 mg daily) as treatment of cryptococcal meningitis in patients with AIDS. A trial comparing various dosages of fluconazole alone with the fluconazole-flucytosine combination has been conducted by the California Collaborative Treatment Group; the results of this study, when published, should help answer questions regarding the appropriate dose of fluconazole for the treatment of cryptococcal meningitis in patients with AIDS.

Fluconazole has found widespread use in the treatment of a variety of different types of candidiasis. It is interesting that, in spite of widespread use, there are few comparative trials proving its equivalence to amphotericin B as treatment of candidal infections. The notable exception is the trial reported by Rex et al. [19] in which fluconazole (400 mg daily) was shown to be as efficacious as amphotericin B (0.5–0.6 mg/[kg · d]) as treatment of candidiasis. It is important to note that this trial excluded patients who were neutropenic, had AIDS, or had received an organ transplant and that ~75% of the patients had indwelling intravenous catheters. Thus, this study showed equivalence of amphotericin B and fluconazole as therapy for this specific population of patients with candidiasia.

A follow-up study is ongoing; in this study, a higher dosage of fluconazole (800 mg daily) is compared with a combination of fluconazole (800 mg daily) with amphotericin B (0.5–0.6 mg/[kg · d]) for the treatment of candidemia. Further studies are needed to define the use of fluconazole for the treatment of candidemia and disseminated candidiasis in other patient groups (e.g., neutropenic patients and patients without intravascular catheters as the likely source of infection). Future studies should also address the usefulness of fluconazole therapy not only for Candida albicans infections but also for infections with other Candida species.

Fluconazole has found an important niche in the treatment of mucocutaneous candidiasis. Several studies have shown that fluconazole over clotrimazole troches as treatment of thrush in patients with AIDS [11, 51]. In addition, fluconazole has been shown to be superior to ketoconazole for the treatment of oropharyngeal and esophageal candidiasis [52, 53]. Fluconazole also has been shown to be useful for the treatment of focal forms of candidiasis [54, 55] and chronic disseminated or hepatosplenic candidiasis [56, 57]. The drug is the preferred treatment of funguria and focal urinary tract infections; however, no comparative data have proved that fluconazole is superior to other forms of therapy [58, 59].

One of the most important uses of fluconazole has been as prophylaxis for patients at risk for serious fungal infections. Fluconazole has been shown to decrease the incidence of both systemic and localized fungal infections in bone marrow transplant recipients [60, 61] and to decrease the incidence of local fungal infections in patients with leukemia [62]. The drug has been frequently used for prophylaxis for patients with AIDS and recurrent episodes of thrush [63], and this very common use may be one of the factors contributing to the increasing problem of azole resistance [15]. A recent prospective, randomized trial with HIV-infected patients [64] showed that 200 mg of fluconazole daily prevented both invasive and superficial fungal infections. However, survival rates were similar among both fluconazole-treated patients and clotrimazole-treated controls, the cost of prophylaxis was high, and increasing use of fluconazole as long-term prophylaxis may lead to increasing problems withazole resistance [11–16].

**Fluconazole Treatment of Endemic Mycoses**

Fluconazole is effective for the treatment of several endemic mycoses, but it is less active than itraconazole as therapy for blastomycosis, histoplasmosis, and sporotrichosis [30, 65, 66]. Fluconazole should be considered as second-line therapy for these diseases and could be used for patients who do not tolerate or cannot absorb itraconazole. The minimum dosage should be 400–800 mg daily.

For patients with coccidioidomycosis, fluconazole is probably as effective as itraconazole for the treatment of nonmeningeal infection [32]. Fluconazole has clearly become the drug of choice for the treatment of coccidioidal meningitis [67]. For most patients with this most serious form of coccidioidomycosis, therapy with oral fluconazole at a minimum daily dose of 400 mg leads to clinical improvement and obviates the need for treatment with intrathecal or intraventricular amphotericin B [32]. Administration of the drug should be continued for life to prevent relapse.

**Drawbacks to the Use of Triazoles**

Fluconazole and itraconazole have enjoyed widespread use, in part because of their ease of administration and the lack of
toxic effects. However, neither drug is the perfect antifungal agent, and both have notable drawbacks [68]. Absorption of itraconazole is problematic. Serum levels are higher when the drug is given with food and when a maximum dose of 200 mg is used for each administration [69]. Drugs that decrease gastric acidity should not be used with itraconazole as absorption may be lessened. Itraconazole and, to a lesser extent, fluconazole are metabolized by cytochrome P-450-dependent enzymes; consequently, drug interactions, which have been reviewed by Como and Dismukes [68], are common and can be potentially life-threatening.

An emerging problem that has arisen only as fluconazole has become more widely used is the development of resistance [15]. Almost unknown before the 1990s, azole resistance has now become a problem for patients with AIDS who are receiving chronic therapy or prophylaxis with fluconazole [11–16]. The incidence of infections with non-albicans species of Candida, such as C. glabrata, that are intrinsically more resistant to fluconazole also appears to be increasing in some hospitals [15, 70–72]. It is not clear whether this increase is due to the pressure of using fluconazole therapy in hospitals. The judicious use of the azole antifungal drugs is clearly beneficial to many patients, but indiscriminate or inappropriate use is associated with the major drawback of increasing antimicrobial resistance.

References