MINIREVIEW

Azole Antifungal Agents: Emphasis on New Triazoles

MICHAEL S. SAAG AND WILLIAM E. DISMUKES*

Division of Infectious Diseases, Department of Medicine, University of Alabama School of Medicine, Birmingham, Alabama 35294,* and Medical Service, Veterans Administration Medical Center, Birmingham, Alabama 35233

Over the last three decades, important progress has been made in the therapy of systemic fungal infections. Although chemotherapeutic agents such as flucytosine and potassium iodide are effective against selected fungal diseases, namely cryptococcosis and sporotrichosis, the primary drugs used to treat systemic mycoses are amphotericin B and the azole compounds. Amphotericin B, a polyene first used clinically in the late 1950s, has become the "gold standard" of systemic antifungal therapy (2). Despite its general effectiveness, amphotericin B is associated with a number of complications and unique toxicities that limit its usage. Furthermore, the drug is poorly absorbed from the gastrointestinal tract, necessitating intravenous administration. In addition, amphotericin B penetrates poorly into cerebrospinal fluid (CSF) of both normal and inflamed meninges; even so, it is the drug of choice for all types of fungal meningitis.

The problems with amphotericin B have stimulated a search for new agents which might be active against a wide range of fungal pathogens, well absorbed after oral administration, widely distributed throughout body tissues including the central nervous system, and relatively nontoxic. As early as 1944, Woolley demonstrated inhibition of fungal growth by benzimidazole, an imidazole compound (63), but it was not until the early 1970s that azole drugs were extensively evaluated for the treatment of systemic mycoses. Clotrimazole was the first oral azole proven to be effective in experimental and human mycoses (1, 38). However, brief courses of treatment with clotrimazole led to the induction of liver microsomal enzymes which in turn increased the metabolism of the drug, thereby diminishing its antifungal activity. Consequently, clotrimazole is now used only as a topical or troche antifungal preparation. In contrast, miconazole, another imidazole which became available for study around the same time as clotrimazole, is not rapidly metabolized and is an effective intravenous therapy for many systemic fungal diseases (1). Unfortunately, the use of miconazole is limited by its multiple toxic effects, many of which are believed to be related to Cremophor EL, a polyethoxylated castor oil that is required for colloidal stabilization of the intravenous compound. Miconazole is used primarily as a topical agent for cutaneous mycoses and as an alternative systemic antifungal agent when amphotericin B or ketoconazole is either ineffective or contraindicated.

Since its development in the late 1970s, ketoconazole has become the most important imidazole antifungal agent, and it represents a major addition to the antifungal armamentarium. Ketoconazole is slightly water soluble and orally

active (Table 1). It also possesses a broad spectrum of antifungal activity based on in vitro and in vivo animal model assays. Peak concentrations in serum 2 to 3 h after ingestion of a 200-mg dose are somewhat variable (2 to 4 $\mu\text{g/ml}$), and concentrations in serum increase linearly with increasing doses (7, 22). However, no correlations between concentrations in serum and clinical efficacy or between MICs and therapeutic effect have been established in either animal models or humans (12, 14, 47). Ketoconazole does not penetrate well into CSF. As opposed to miconazole, the adverse effects associated with ketoconazole are modest and consist primarily of dose-related nausea or vomiting. Elevation in serum transaminases is seen in 1 to 10% of patients, although clinical hepatitis is rare (12, 30). Retrospective reviews have estimated the incidence of ketoconazole-related symptomatic hepatic dysfunction at 1 in 10,000 to 15,000 patients (26, 30). Dose-related inhibition of testosterone synthesis may result in gynecomastia, menstrual irregularities, sexual impotence, azoospermia, or oligospermia (9, 39, 40). The drug also may interfere in a dose-related manner with adrenal corticosteroid synthesis (39, 41), although to our knowledge only one case of clinically apparent adrenal insufficiency has been reported (53). In addition to its potential toxicity, several well-described drug interactions with ketoconazole have been documented. The two results that have received the most attention are the significant decrease in the levels of ketoconazole in plasma when the drug is given simultaneously with rifampin (16) and prolongation of the half-life of cyclosporin A when that drug is given concomitantly with ketoconazole (H. Dieperink and J. Moller, Letter, *Lancet* ii:1217, 1982). Ketoconazole, even after a prolonged period of administration, does not appear to induce liver microsomal enzymes. Clinical trials have established ketoconazole as the drug of choice for nonimmunocompromised individuals with non-life-threatening blastomycosis (12), chronic mucocutaneous candidiasis (24, 37), histoplasmosis (12), and paracoccidioidomycosis (42, 43). Ketoconazole also has some efficacy in selected forms of coccidioidomycosis (49; J. N. Galgiani, D. A. Stevens, J. R. Graybill, W. E. Dismukes, G. A. Cloud, and the NIAID Mycoses Study Group, submitted for publication) and candidiasis (13).

Even with the advent of ketoconazole, the search for improved antifungal azole agents has continued due in part to concerns over the potential for toxicity and poor penetration into CSF of ketoconazole. Several newer azoles have been developed as topical agents primarily directed at superficial candidal and dermatophytic infections. Most recently, two new investigational triazole compounds, itraconazole and fluconazole, have shown promise as systemic antifungal

* Corresponding author.

TABLE 1. Pharmacologic properties^a

Agent (reference[s])	Mol wt	Water solubility	% Protein bound	AUC ($\mu\text{g} \cdot \text{h/ml}$)	Relative bioavailability (%)	% Urinary excretion (active drug)	$t_{1/2\beta}$ (h)	C_{max} ($\mu\text{g/ml}$)	T_{max} (h)	% CSF/serum concn ^b
Ketoconazole (7, 22)	531	Poor	99	12.9 (13.6) ^c	75	2	8.1	3.29	2.620	<10
Itraconazole (23, 55)	706	Poor	99.8	1.9 (0.7) ^c	99.8 (40) ^c	<1	17	0.132	4.0	<10
Fluconazole (25)	305	Good	11	42 ^d	85 ^d	64	22	1.4	1.0-4.0	>60

^a AUC, Area under the curve; $t_{1/2\beta}$, half life at elimination phase; C_{max} , maximum concentration in plasma; T_{max} , time to maximum concentration.

^b Reference 35.

^c With meal (fasting).

^d Fasting.

agents. The remainder of this review focuses on these two agents.

TRIAZOLE AGENTS

Structure. The basic structural unit of all of the antifungal azoles is a five-membered azole ring which is attached by a carbon nitrogen bond to other aromatic rings (Fig. 1). Imidazole drugs contain two nitrogen atoms in the azole ring. In contrast, the triazole class of agents contains a third nitrogen atom in the azole ring.

Mechanism of action. The molecular mechanisms of action of the triazole agents appear similar to those of the antifungal imidazoles. Active investigation over the last decade has revealed several unique sites of antifungal activity of azole compounds within the metabolic pathways of fungi. The primary mechanism of action is inhibition of ergosterol biosynthesis with resultant accumulation of 14 α -methylsterols, the precursor intermediates of ergosterol (4, 59, 61, 62). The demethylation step required to convert 14 α -methylsterols to ergosterol has been shown to be dependent on cytochrome P-450 activation. At the molecular level, one of the nitrogen atoms (N-3 in the imidazoles; N-4 in the triazoles) binds to the heme iron of cytochrome P-450, thereby inhibiting cytochrome activation and enzyme function (59, 60, 62). In contrast to miconazole and ketoconazole, itraconazole binds weakly to mammalian cytochrome P-450 while maintaining a high affinity for fungal P-450 enzymes (60). Other antifungal effects of the azole compounds have been observed. High imidazole concentrations have been associated with rapid fungicidal activity that could

not be explained by the inhibition of sterol synthesis alone (50, 54). This antifungal effect was believed to be due to direct membrane damage via primary attack of drug on membrane phospholipids. Azole compounds also may inhibit cytochrome *c* oxidative and peroxidative enzymes, with resultant increase in intracellular peroxide generation (11, 48, 54). Finally, very low concentrations of imidazole agents have been shown to inhibit the morphogenetic transformation of candidal yeast forms to pseudohyphae, which appear to be directly toxic to leukocytes and macrophages (8, 27).

In vitro antifungal activity. The in vitro antifungal activities of itraconazole and fluconazole have been studied by a number of investigators (17, 19, 21, 28, 34, 36, 46, 57, 58). Direct comparisons of MIC data from one study to another or one drug to another are complicated by variability in testing methods and the lack of standardized approaches, especially with respect to the growth medium used (including pH) and the size of the inoculum. In addition, the newer antifungal agents often cause a gradual diminution of growth in the presence of increasing drug concentration rather than having a sharp, well-defined endpoint, thereby making it difficult to determine precise MICs. As a result, the wide ranges of MICs reported, even within individual studies, hamper conclusions regarding the antifungal activity of a given agent against a specific pathogen. Moreover, the reproducibility of MIC antifungal testing and its clinical predictability have been questioned (28, 34). Consequently, in vivo animal models of fungal infections appear to provide better means of assessing the relative antifungal effectiveness of the new triazole agents.

FIG. 1. Structures of representative antifungal azole compounds.

ITRACONAZOLE

Antifungal activity in in vivo animal models. As shown in Table 2, itraconazole has been evaluated in a number of models of systemic fungal infections in mice, guinea pigs, and rabbits and shown to be clinically and microbiologically active against a variety of pathogens, including *Aspergillus* species, *Candida albicans*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Sporothrix schenckii*. In general, the animal in vivo activity tends to parallel the activity shown by in vitro susceptibility testing.

Pharmacologic properties. Itraconazole is a lipophilic compound that is characterized by good absorption after oral administration, extensive distribution in tissues, and a relatively long serum half-life. The drug is degraded into a number of inactive metabolites which are excreted primarily

in bile and urine. A comparison of the pharmacologic properties of ketoconazole, itraconazole, and fluconazole is shown in Table 1. Like ketoconazole, itraconazole is better absorbed following a meal than in the fasting state, as demonstrated by the area under the curve and bioavailability data (5, 7, 57). After oral doses of 50, 100, and 200 mg, increases in the area under the curve are more than proportional, suggesting that higher doses transiently saturate hepatic metabolic processes, with resultant augmentation of bioavailability (23). Normal volunteers who received repetitive oral administration of itraconazole, 100 mg/day, achieved steady state in 10 to 14 days. The area under the curve values were increased fourfold over the single-dose area under the curve value, and the peak concentrations were two- to threefold higher than the single-dose values (23).

Itraconazole is widely distributed throughout body tissues, with approximately 20 times the volume of distribution

TABLE 2. In vivo activity of itraconazole in experimental animal models of systemic fungal diseases

Reference	Organism	Animal	Route of infection ^a	Treatment regimen		Outcome
				Daily dose (mg/kg)	Route ^b	
20	<i>Aspergillus fumigatus</i>	Mouse	i.n.	70	p.o.	No benefit
		Mouse	i.v.	70	p.o.	Prolonged survival; itraconazole = amphotericin B Reduced colony counts; itraconazole = amphotericin B
58	<i>A. fumigatus</i>	Mouse	i.v.	40	p.o.	Prolonged survival
				80	p.o.	Prolonged survival; 6 of 14 survivors culture negative
36	<i>Candida albicans</i>	Rabbit	i.v.	50	p.o.	Reduced colony counts in kidney, dose related
				200	p.o.	
56	<i>C. albicans</i>	Guinea pig	i.v.	5, begun day 0	p.o.	Cured or improved, 100%; negative kidney cultures, 96%
57	<i>C. albicans</i>	Guinea pig	i.v.	5, begun day 2	p.o.	Cured or improved, 83%; negative kidney cultures, 50%
	<i>C. albicans</i>	Mouse	i.v.	40	p.o.	Improved survival, 55%
29	<i>Coccidioides immitis</i>	Mouse	i.n.	15-50	p.o.	Reduced colony counts; itraconazole = ketoconazole
19	<i>Cryptococcus neoformans</i>	Mouse	i.p.	60	p.o.	Prolonged survival; itraconazole = ketoconazole
		Mouse	i.c.	60	p.o.	Prolonged survival; itraconazole = ketoconazole; positive brain cultures, all survivors; reduced colony counts, itraconazole > ketoconazole
36	<i>C. neoformans</i>	Rabbit	i.c.	80	i.v.	Reduced CSF colony counts; 11 of 14 animals culture negative; itraconazole = fluconazole
57	<i>C. neoformans</i>	Mouse	i.c.	160	p.o.	Prolonged survival; itraconazole > ketoconazole
57	<i>Histoplasma capsulatum</i>	Guinea pig	i.t.	10	p.o.	Reduced colony counts; cure, 63%
				40	p.o.	Clinical and cultural cure, 100%
32	<i>Paracoccidioides brasiliensis</i>	Mouse	i.n.	10	p.o.	Prolonged survival; itraconazole > ketoconazole; persistent lung infection
57	<i>Sporothrix schenckii</i>	Guinea pig	i.t.	10	p.o.	No dissemination; negative cultures, 30%
				40	p.o.	No dissemination; negative cultures, 100%

^a i.n., Intranasal; i.v., intravenous; i.p., intraperitoneal; i.c., intracerebral; i.t., intratesticular.

^b p.o., Per os; i.v., intravenous.

of ketoconazole. Due to the drug's high binding to plasma proteins (less than 0.2% free drug in plasma), concentrations of itraconazole in body fluids, such as saliva and bronchial secretions, are less than 1 µg/ml (23). In addition, itraconazole penetrates poorly into CSF whether or not meninges are inflamed (35). In contrast, tissue concentrations in the lung, kidney, brain, and epidermis are two- to fivefold greater than in plasma (57). These findings imply better bioavailability of itraconazole at the sites of most fungal disease, except the meninges.

Studies suggest that no dose adjustment is necessary in patients with liver impairment or renal insufficiency (23). In addition, no effect on the clearance of concomitantly administered agents, such as warfarin anticoagulants, cyclosporin A, insulin, or antipyrine, has been demonstrated (23). However, as with ketoconazole, rifampin when coadministered with itraconazole does appear to reduce the bioavailability of itraconazole.

Clinical studies. Itraconazole is effective therapy for numerous superficial fungal diseases, including pityriasis versicolor, candidal vaginal and oral infections, and dermatophytic infections; however, the focus here is on systemic mycoses. Preliminary reports indicate that itraconazole in doses of 50 to 400 mg/day may be effective therapy for blastomycosis, histoplasmosis, paracoccidioidomycosis, chromomycosis, sporotrichosis, and coccidioidomycosis (3, 6, 33). Among 12 patients with blastomycosis, 6 of whom had failed ketoconazole therapy, all were cured with itraconazole at 200 mg/day (R. W. Bradsher, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1351, 1987). In another study of blastomycosis, 12 patients received at least 3 months of therapy (200 to 400 mg/day) and all were considered cured. Seventeen patients are still on treatment (W. Dismukes, R. Bradsher, W. Girard, M. Saag, S. Chapman, G. Karam, D. Stevens, C. Kauffman, C. Gregg, S. Shadomy, and the NIAID Mycoses Study Group, 26th ICAAC, abstr. no. 798, 1986). In the same study, among 12 patients with histoplasmosis (primarily pulmonary disease), 9 have completed 3 or more months of therapy (200 to 400 mg/day). Six are considered cured, and one has relapsed (after receiving 6 months of treatment). In a second study of 17 patients with chronic pulmonary or chronic disseminated forms of histoplasmosis, 15 patients received at least 3 months of itraconazole therapy at 50 to 100 mg/day (33). Fifteen patients were cured or improved, one relapsed, and one died.

Itraconazole therapy of paracoccidioidomycosis has been evaluated in two studies involving 41 patients; 27 were treated with 50 to 100 mg/day for 6 or more months, and 14 were treated for ≤3 months (33, 44). Thirty-nine patients (95%) were cured or improved. In patients with chromomycosis, infections with *Cladosporium* species were associated with a higher cure rate than those with *Fonsecaea* species (6). Of 31 patients with sporotrichosis treated with itraconazole (100 mg/day) for 3 to 6 months, 30 were cured or improved (6). The data on itraconazole therapy of serious, invasive *Candida* infections in humans are limited, although the drug does appear to be effective in esophageal candidiasis (G. Cauwenbergh, Presentation, Annu. Meet. Danish Soc. Mycopathol. 1986).

Treatment of coccidioidomycosis with itraconazole has required higher doses to achieve significant clinical responses. In an ongoing study of 50 patients with generally severe disease (prior relapse in 58% of patients), 7 or more months of therapy with itraconazole at doses of 200 to 400 mg/day has been necessary to achieve greater than 50%

improvement in mean severity-of-disease scores compared with pretreatment evaluation scores (J. R. Graybill, D. A. Stevens, J. N. Galgiani, W. E. Dismukes, G. Cloud, A. Ganer, E. Arathoon, R. Fetchick, M. Diaz, and the NIAID Mycoses Study Group, 26th ICAAC, abstr. no. 788, 1986). Another study noted similar improvement in patients with coccidioidomycosis treated with higher doses of itraconazole (18).

Although the antifungal imidazoles, miconazole and ketoconazole, have not been especially effective for aspergillosis and cryptococcosis, itraconazole does show promise as therapy for these two diseases. Preliminary data from two studies indicate that itraconazole in doses of 200 mg/day led to improvement in 11 of 14 patients with invasive or presumed invasive aspergillosis (6, 15). Among a larger series of 19 patients treated with itraconazole for invasive aspergillosis, only 8 were cured or improved (Cauwenbergh, Annu. Meet. Danish Soc. Mycopathol.). Nineteen patients with cryptococcal meningitis have been treated with itraconazole, 100 to 200 mg/day, with limited success (Cauwenbergh, Annu. Meet. Danish Soc. Mycopathol.). Of particular interest, three acquired immunodeficiency syndrome (AIDS) patients with cryptococcal meningitis have been treated with long-term suppressive itraconazole therapy (M. A. Viviani, A. M. Tortorano, P. C. Giani, C. Arici, A. Goglio, P. Crocchiolo, M. Almaviva, Letter, Ann. Intern. Med. 106: 166, 1987). Clinical improvement was noted in all three patients, and cultures converted from positive to negative. One of the patients, who later died of cytomegalovirus pneumonia, had no cultural or histologic evidence of cryptococcosis at autopsy.

Toxicity. On the basis of the preliminary reports of itraconazole therapy for mycotic diseases in humans, toxicity has been minimal. Various degrees of nausea have been reported in 1 to 20% of drug recipients, and asymptomatic transient hepatic enzyme elevations have been noted in <5%. Of note, hypokalemia and/or pedal edema have been observed in a few patients, although the mechanism for these adverse effects remains unknown (A. Ganer, E. Arathoon, and D. A. Stevens, 26th ICAAC, abstr. no. 799, 1986; Graybill et al., 26th ICAAC, abstr. no. 788, 1986). Studies to date in both animals and humans have failed to demonstrate any adverse effect of itraconazole on testicular or adrenal steroidogenesis (55). Among human volunteers given itraconazole daily for 2 weeks, there was no change in testosterone and cortisol levels compared with pretreatment values. Interestingly, among 27 male patients treated for histoplasmosis or blastomycosis, 3 reported impotence and/or decreased libido; however, in all 3, serum testosterone concentrations during therapy were normal (unpublished data).

FLUCONAZOLE

Antifungal activity in in vivo animal models. Fluconazole has been shown to be efficacious in in vivo animal model infections of aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, and histoplasmosis (Table 3). In contrast to itraconazole, the in vitro activity of fluconazole against selected pathogens does not parallel its activity in in vivo animal model infections with the same organisms. In general, the MICs of fluconazole in most susceptibility testing systems are much higher than would be predicted for an effective antifungal agent (21, 28, 46). For example, by in vitro testing, ketoconazole was 16-fold more active against *Candida* species than fluconazole, yet fluconazole was 24-fold more effective than ketoconazole when

TABLE 3. In vivo activity of fluconazole in experimental animal models of systemic fungal diseases

Reference	Organism	Animal	Route of infection ^a	Treatment regimen		Outcome
				Daily dose (mg/kg)	Route ^b	
52	<i>Aspergillus</i> sp.	Mouse	i.v.	100	p.o.	<i>A. flavus</i> , fluconazole > ketoconazole; <i>A. fumigatus</i> , amphotericin B > fluconazole
31	<i>Blastomyces dermatitidis</i>	Mouse	i.n.	5 50	s.c. s.c.	No benefit Prolonged survival; negative cultures, 66% (amphotericin B) and none (fluconazole)
Stevens et al. ^c	<i>B. dermatitidis</i>	Mouse	i.n.	10 100	p.o. p.o.	Prolonged survival, fluconazole (100 mg/kg) > fluconazole (10 mg/kg) > ketoconazole (100 mg/kg)
36	<i>Candida albicans</i>	Rabbit	i.v.	10 80	i.v. i.v.	Reduced colony counts, dose related
45	<i>C. albicans</i>	Mouse, rat	i.v.	0.01–2.0	p.o., i.v.	50% Effective dose: amphotericin B > fluconazole > ketoconazole
46	<i>C. albicans</i>	Rat	i.v.	0.5	p.o.	Prolonged survival; fluconazole > ketoconazole
51	<i>C. albicans</i>	Mouse	i.v.	2.0	p.o.	Prolonged survival; fluconazole > ketoconazole
Fisher et al. ^d	<i>C. albicans</i>	Rat	i.v.	20 40	p.o. p.o.	Reduced colony counts, dose related; amphotericin B > fluconazole
Graybill et al. ^e	<i>Coccidioides immitis</i>	Mouse	i.c.	40 120	p.o. p.o.	Prolonged survival, amphotericin B > fluconazole (120 mg/kg) > fluconazole (40 mg/kg) = ketoconazole (120 mg/kg)
Levine ^f	<i>C. immitis</i>	Mouse	i.n.	40	p.o.	Prolonged survival; fluconazole = ketoconazole
10	<i>Cryptococcus neoformans</i>	Mouse	i.n.	40	p.o.	Prolonged survival; persistent positive cultures
36	<i>C. neoformans</i>	Rabbit	i.c.	80	i.v.	Reduced colony counts; 4 of 7 animals culture negative; fluconazole = intraconazole
52	<i>C. neoformans</i>	Mouse, athymic mouse	i.c.	5	p.o.	Prolonged survival; persistent positive brain cultures
21	<i>Histoplasma capsulatum</i>	Mouse	i.n.	60	p.o.	Prolonged survival; fluconazole = amphotericin B Reduced lung colony counts; amphotericin B > fluconazole
		Athymic mouse	i.n.	40	p.o.	Prolonged survival and reduced colony counts; fluconazole = amphotericin B
28	<i>H. capsulatum</i>	Mouse	i.v.	Variable	p.o.	50% Protective dose, amphotericin B > fluconazole; therapeutic:toxic ratio, fluconazole > amphotericin B
Stevens et al. ^c	<i>Paracoccidioides brasiliensis</i>	Mouse	i.n.	50 100	p.o.	Complete protection against lethal challenge; reduced colony counts, fluconazole > ketoconazole

^a i.v., Intravenous; i.n., intranasal; i.c., intracerebral.^b p.o., Per os; s.c., subcutaneous; i.v., intravenous.^c D. A. Stevens, E. Brummer, J. G. McEwen, and A. Perlman, unpublished data.^d M. Fisher, W. Tarry, P. G. Lee, S. Padden, and C. O'Brien, 27th ICAAC, abstr. no. 776, 1987.^e J. R. Graybill, J. Ahrens, and S. H. Sun, 25th ICAAC, abstr. no. 921, 1985.^f H. B. Levine, 26th ICAAC, abstr. no. 786, 1986.

tested in an in vivo model of systemic candidiasis using the same organism (46). The same discrepancy between in vitro and in vivo activity was observed in studies with *H. capsulatum* (21, 28).

Pharmacologic properties. Fluconazole differs markedly in its pharmacology and pharmacokinetic profile from other antifungal azole compounds (Table 1). It is water soluble, is

weakly protein bound with a high bioavailability, penetrates well into CSF, and is excreted unchanged in the urine in high concentrations. In contrast to ketoconazole and itraconazole, fluconazole is metabolically stable, with recovery of over 90% of the administered dose unchanged in urine and feces.

In studies in human volunteers, absorption after oral

administration is good; relatively high concentrations in plasma are achieved, e.g., 1.4 µg/ml after a 1-mg/kg (body weight) dose. The volume of distribution (1 liter/kg) combined with 11% protein binding results in high free-drug concentrations throughout the body. In addition, autoradiographic studies in mice demonstrate even distribution of drug throughout all body tissues (25). These data suggest that fluconazole may be effective against infections in a number of organ systems, such as the gastrointestinal tract, urinary tract, and central nervous system.

Perhaps the most striking difference between fluconazole and other azole compounds is its penetration into the CSF (Table 1). Concentrations in CSF are generally 60 to 80% of levels in serum in the presence of uninflamed and inflamed meninges, respectively (36; R. M. Tucker, P. L. Williams, B. E. Levine, A. I. Hartstein, L. Hanson, and D. A. Stevens, 27th ICAAC, abstr. no. 777, 1987).

Multiple-dose studies with fluconazole (50 mg/day) have shown slight accumulation of drug over time with peak levels in plasma of 1.05, 2.21, 2.37, and 2.62 µg/ml on days 1, 7, 14, and 28, respectively (*Pfizer Central Research Investigators' Reference Manual*, 1986). Steady state was achieved by dose 5, and the serum elimination half-lives at the end of days 7 and 26 were 23.8 and 28.6 h, respectively, compared with the single-dose half-life of 22 h. Dosage reduction is required in individuals with renal impairment. Data about possible interactions of fluconazole with other drugs are not available. An intravenous formulation of fluconazole is under study.

Clinical studies. Fluconazole appears to be an effective agent for the therapy of dermatomycoses and oral and vaginal candidiasis (*Pfizer Central Research Investigators' Reference Manual*, 1986; P. R. Farrow, K. W. Brammer, and J. M. Feczko, 27th ICAAC, abstr. no. 949, 1987; K. W. Brammer and J. M. Feczko, 27th ICAAC, abstr. no. 43, 1987). However, little information is available regarding the efficacy of fluconazole therapy for systemic mycoses. Some perspective is provided by preliminary results of ongoing phase II clinical trials by the National Institute of Allergy and Infectious Diseases Mycoses Study Group (unpublished data). All patients have received fluconazole in daily doses of 50 to 100 mg; these low doses were mandated because of limited animal toxicity data and in vivo phase I human data available at the start of the trials. Among eight patients with histoplasmosis treated from 1 to 12 months, three have failed. Two patients with sporotrichosis have been treated, but only one has responded. In a group of 15 patients with blastomycosis treated for periods ranging from 1 to 12 months, fluconazole at 50 to 100 mg/day has been ineffective. Disease progression has been observed in eight patients. Among a cohort of 20 patients with chronic pulmonary, soft tissue, or bone or joint forms of coccidioidomycosis, fluconazole has been administered for periods ranging from 2 to 12 months. Thus far, nine patients have failed. Although definitive comments about efficacy cannot be made, since many of the patients remain on therapy and adequate post-treatment follow-ups are not available, it appears that fluconazole in doses of 50 to 100 mg/day is inadequate therapy for the systemic mycoses mentioned above.

Fifteen patients with CSF culture-positive acute cryptococcal meningitis have been treated with fluconazole at 50 to 200 mg/day (unpublished data). While data are incomplete and preliminary, the drug in the doses used has given encouraging results. Conversion of CSF cultures from positive to negative has been observed in 11 patients. A small cohort of patients with AIDS complicated by cryptococcal

meningitis has received maintenance fluconazole therapy in an attempt to prevent relapse (J. Stern, K. Sharkey, B. Hartman, and J. Graybill, 27th ICAAC, abstr. no. 948, 1987). Outcomes are not yet evaluable. A large, prospective, multicenter, randomized trial to compare fluconazole and amphotericin B as maintenance or suppressive therapy in AIDS patients with cryptococcal meningitis has been initiated by the National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Treatment Evaluation Units. In addition, a smaller, prospective, multicenter, dose-ranging efficacy study of fluconazole as primary therapy for cryptococcal meningitis in patients with AIDS is planned. In these studies of cryptococcosis, as well as in new studies of other systemic mycoses, 200- to 400-mg/day doses of fluconazole will be used.

Toxicity. More than 2,000 volunteers or patients (primarily treated for candidiasis or dermatophytic infection) have received fluconazole in doses of 50 to 100 mg/day for periods ranging from 1 to 42 days. The drug has been very well tolerated. Nausea, other minor gastrointestinal symptoms, and asymptomatic elevations of hepatic enzymes have been reported in less than 5% of drug recipients. In the 50 patients treated with fluconazole in the Mycoses Study Group ongoing trials, the drug has also been well tolerated; nausea has been the most common side effect. Adverse effects related to possible inhibition by fluconazole of testosterone and steroid synthesis have not been observed.

SUMMARY

Many advances have been made in antifungal therapy over the last three decades. Itraconazole and fluconazole, two investigational triazole agents, are the most recent additions to the list of antifungal drugs. This review has focused primarily on their mechanisms of action, favorable pharmacologic properties, and spectra of activity against a broad range of systemic pathogens. Itraconazole and fluconazole show much promise as orally active agents, with less potential for toxicity than the currently available azoles. Fluconazole and, to a lesser degree, itraconazole are especially promising therapies for cryptococcal meningitis. In addition, fluconazole may prove to be highly effective in urinary tract infections caused by *Candida* species and other fungi. Ongoing and future clinical trials will more clearly define the specific roles of itraconazole and fluconazole in the treatment of systemic mycoses.

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