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The role of azole antifungal agents for systemic antifungal therapy

KEY POINTS:

Amphotericin B remains the first-line agent for serious fungal infections in most patients, including immunocompromised patients (eg, those with AIDS) and in central nervous system infections.

The overall prevalence of resistance to azole agents is low. The only exception is in AIDS patients, in whom resistance is much higher than in other populations, and is increasing.

Azole agents can increase the concentration of phenytoin, cisapride, oral glucose-lowering agents, warfarin, digoxin, terfenadine, astemizole, and cyclosporine, potentially leading to toxicity.

ABSTRACT: Although amphotericin B remains the cornerstone of antifungal drug therapy, fluconazole and itraconazole have been found useful for long-term maintenance or prophylactic regimens. This article reviews characteristics of fluconazole and itraconazole and compares them with ketoconazole and amphotericin B.

Ketoconazole, fluconazole, and itraconazole have not supplanted amphotericin B for managing most serious fungal infections, but they offer alternatives in a variety of unique situations. These drugs (the "azoles") are becoming standard as antifungal prophylactic agents in transplant recipients and as long-term suppressive agents for cryptococcal meningitis in patients with acquired immunodeficiency syndrome (AIDS). Fluconazole may also be useful in treating AIDS-related candidemia. Itraconazole and ketoconazole are both effective for blastomycosis, histoplasmosis, and coccidiomycosis. The azoles are significantly less nephrotoxic than amphotericin B, but are not without side effects. They also demonstrate a number of significant drug interactions.

HISTORY OF THE AZOLES

Miconazole, the first systemic azole agent, was introduced in 1969. However, its toxicity, side effects (especially arrhythmia), and poor efficacy limit its use.

Ketoconazole, introduced in 1977, was the first oral azole agent. It is not active against *Aspergillus*, but otherwise shares a similar spectrum of action with amphotericin B.

Fluconazole was introduced in 1990 and quickly became popular

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owing to its attractive pharmacokinetic and side-effect profiles and its availability in intravenous and oral formulations.

Itraconazole was introduced in 1992. It is active against *Aspergillus* and has fewer side effects than ketoconazole.

HOW THE AZOLES WORK

The azoles alter fungal membrane permeability by inhibiting fungal cytochrome P450 and C-14 alpha-demethylase[1,2]—enzymes shared by humans. Fluconazole and itraconazole act more specifically on the fungal enzymes than ketoconazole does, and therefore cause less blockage of human steroid synthesis and fewer side effects.[1,3]

PHARMACOKINETICS

Fluconazole is highly bioavailable; others less so

Over 90% of an oral dose of fluconazole reaches the blood stream, perhaps owing to its relatively high water solubility and low molecular weight. Neither food nor gastric pH affects fluconazole's absorption.

In contrast, oral doses of ketoconazole and itraconazole are less bioavailable, with 37% to 97% of ketoconazole and 70% of itraconazole reaching the blood stream. Giving these drugs with food enhances their systemic absorption, especially itraconazole. Gastric pH affects the absorption of both agents, with a lower pH allowing improved absorption.

Giving terfenadine or astemizole with itraconazole or ketoconazole is contraindicated because of the potential for serious cardiovascular events

Ketoconazole and itraconazole are highly protein-bound; fluconazole less so

Ketoconazole and itraconazole are highly bound to plasma proteins (98% and 99.8%, respectively), and therefore are not significantly dialyzable and achieve relatively low levels in the cerebrospinal fluid. Nevertheless, itraconazole has been reported effective in treating cryptococcal and coccidioidal meningitis, a paradox similar to that seen with amphotericin B.

Fluconazole is more hydrophilic and has a low degree of protein binding. It is therefore dialyzable, and patients need dosage adjustment after dialysis. Fluconazole enters the cerebrospinal fluid easily, where concentrations reach 50% to 90% of the plasma concentration.

Ketoconazole, itraconazole are metabolized in the liver; fluconazole is excreted by the kidneys

Ketoconazole and itraconazole undergo extensive metabolism by the cytochrome P450 system in the liver (more than 30 metabolites of itraconazole have been reported).

Fluconazole, in contrast, is primarily excreted unchanged by the kidneys. Patients with renal insufficiency require dosage adjustments with fluconazole but not with itraconazole or ketoconazole.

SPECTRUM OF ACTIVITY

Ketoconazole, fluconazole, and itraconazole are all active in vitro against *Cryptococcus neoformans*, *Candida albicans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis*. Both fluconazole and itraconazole—but not ketoconazole—are active against *Sporothrix schenckii*. Itraconazole is the only currently available azole agent that covers *Aspergillus*. Fluconazole is less active against *Candida glabrata* and inactive against *Candida krusei*.[4]

THERAPEUTIC ROLES

Amphotericin B still the drug of choice

Amphotericin B remains the drug of choice for serious systemic fungal infections (**TABLE 1**). It is also the first-line agent for serious fungal infections in immunocompromised patients (eg, those with AIDS) and central nervous system infections.[5–7] In coccidioidomycosis meningitis, amphotericin B is often given intravenously and intrathecally.[6]

In studies in non–AIDS-related cryptococcal meningitis, adding flucytosine to amphotericin B boosted the cure rate and reduced the rates of treatment failure and relapse.[8,9] However, for AIDS-related cryptococcal meningitis, amphotericin B is suggested by itself, since adding flucytosine has not been

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shown to increase the survival rate or to decrease the relapse rate of infection.[10]

Ketoconazole

Ketoconazole is the drug of choice for *Malassezia furfur* infections.[6] Other uses:

- In blastomycosis and coccidioidomycosis (high doses recommended).[11,12]
- In histoplasmosis and paracoccidioidomycosis (in which its efficacy is comparable to that of itraconazole).[4,13–16]
- As prophylaxis in neutropenic patients[17–20] (although its role is not well defined, because its absorption is erratic).
- In severe recalcitrant cutaneous dermatophyte infections not responding to topical therapy or oral griseofulvin or in patients unable to take griseofulvin.[2]

Fluconazole

Fluconazole has no effect against *Aspergillus* or C *krusei*, and is not very potent against blastomycosis,[21,22] chromoblastomycosis,[23] or *Penicillium marneffei*.[24] It has variable efficacy against C *glabrata*.

Candidal infections. Fluconazole is useful in several situations:

- As prophylaxis against candidal infections in bone-marrow transplant recipients, who receive cytotoxic chemotherapy or radiation therapy.[25–28]
- In oropharyngeal and esophageal candidiasis (in which it is the drug of choice, and several studies evaluated it in patients with AIDS).[29–32]
- In urinary candidiasis (drug of choice).[33,34]
- In vaginal candidiasis (drug of choice).[33,35–38]
- In systemic candidal infections (although fluconazole was as effective as amphotericin B for candidemia, the studies were limited to catheter-related infections or included patients treated with amphotericin B for prolonged periods before starting fluconazole).[39–41]

Cryptococcal infections. Fluconazole is an alternative to amphotericin B in clinically stable patients without AIDS who have cryptococcal infections. In one study, fluconazole was as effective as amphotericin B in treating cryptococcal meningitis, but it was associated with a higher mortality rate during the first 2 weeks of therapy.[42] Cerebrospinal fluid cultures remained positive for *Cryptococcus* significantly longer with fluconazole than with amphotericin (40.6 days vs 15.6 days).[43]

Prophylactic use. Prudent use in bone marrow transplant recipients is warranted,[44–51] even though excessive use of fluconazole can lead to drug resistance: an increased emergence of C *krusei* and C *glabrata* infections

TABLE 1

ANTIMICROBIAL EFFECTIVENESS OF AZOLE AGENTS AND AMPHOTERICIN B

Type of infection	Amphotericin B	Ketoconazole	Fluconazole	Itraconazole
Aspergillosis	+++	0	0	++
Blastomycosis				
Immunocompetent patients	++++	+++	0 to +	+++
Immunosuppressed patients	++++	++ to +++	0 to +	+++
Candidiasis				
Blood	++++	+	+++	?
Oropharyngeal, esophageal	?	++	+++	+++
Urinary	?	?	+++	?
Vaginal	?	+++	+++	++ to +++
Prophylaxis	?	?	+++	?
Chromoblastomycosis	++	++	0 to +	+++
Coccidiomycosis				
Nonmeningitis	+++	+++	++	+++
Meningitis	+++	++ to +++	++ to +++	++ to +++
Cryptococcal				
Non-AIDS patients	++++	0	+++	?
AIDS patients	++++	0	++ to +++	++
Maintenance therapy	++	?	++ to +++	+++
Histoplasmosis	++++	+++	++	+++
Leishmaniasis	+++	++	?	++
Malassezia furfur infection	?	++ to +++	?	++ to +++
Neutropenic prophylaxis	+++	++ to +++	+++	++ to +++
Onychomycosis	?	+++	+++	+++
Paracoccidioidomycosis	+++	+++	?	+++
Penicillium marneffei infection	+ to ++	?	0 to +	+ to ++
Sporotrichosis	++	0	+ to ++	++

Scale:
0 Not effective
\+ Less effective
++ Moderately effective
+++ Effective
++++ Very effective
? Not yet established

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TABLE 2

ADVERSE REACTIONS TO AZOLE AGENTS

Frequency	Reactions		
	Ketoconazole	Fluconazole	Itraconazole
Very common (> 10%)	—	—	Nausea
Common (1–10%)	Abdominal pain Asymptomatic liver dysfunction (2-12%) Nausea Pruritus Vomiting	Abdominal pain Asymptomatic liver dysfunction (< 5%) Diarrhea Headache Nausea Skin rash Vomiting	Abdominal pain Asymptomatic liver dysfunction (0.3-2.7%) Headache Rash Vomiting
Less common (< 1%)	Bulging fontanelles Chills Diarrhea Dizziness Fever Gynecomastia Headache Hemolytic anemia Impotence Leukopenia Photophobia Somnolence Thrombocytopenia	Dizziness Hypokalemia Pallor	Anorexia Decreased libido Diarrhea Dizziness Edema Fatigue Fever Hypertension Hypokalemia Impotence Malaise Pruritus Somnolence
Rare	—	Severe hepatotoxicity	—

has been reported.[44,45] Nevertheless, drug resistance has not been a major problem.

Itraconazole

Itraconazole can be used to treat pulmonary and extrapulmonary aspergillosis in patients who cannot tolerate amphotericin B, or for whom amphotericin B fails.[52] Other uses are shown in **TABLE 1**. Some clinicians prefer itraconazole to ketoconazole because it has fewer side effects, even though it is more expensive.

Itraconazole has also been used for neutropenic prophylaxis. Failures, however, have been reported in bone marrow transplant and AIDS patients when serum concentrations were less than 250 ng/mL.[53,54] This may be because of decreased itraconazole absorption due to changes in gastric pH.

Itraconazole is also effective in treating superficial dermatomycoses,[55] as it persists in the skin, nails, and hair follicles at therapeutic levels for weeks after discontinuation. However, whether it offers any significant advantage over ketoconazole, fluconazole, or clotrimazole for treating superficial infections remains unclear.

MICROBIAL RESISTANCE

The overall prevalence of resistance to azole agents is low.[46,47,51] The only exception is in AIDS patients, in whom resistance is much higher than in other populations (33% vs 11%)—and increasing.[56] As mentioned above, resistant strains of *C krusei* and *C glabrata* have emerged with incremental use of fluconazole.[45,57] Resistant strains of *C neoformans* have been reported in AIDS populations.[58]

Amphotericin B remains very active against many species, with no resistance by candidal species being reported.[59] The only organisms reported resistant to amphotericin B are *Pseudallescheria boydii* and *Trichosporon beigelii*.[59–61]

Tests of antifungal susceptibility correlate poorly with clinical outcome; an exception may be in HIV patients with *Candida* infections.[62,63]

ADVERSE DRUG REACTIONS

TABLE 2 summarizes adverse drug reactions associated with ketoconazole, fluconazole, and itraconazole. Endocrine effects such as gynecomastia, decreased libido, and impotence are more frequent with ketoconazole than with itraconazole or fluconazole, because of ketoconazole's less-specific binding to human steroids.[4]

Use in pregnancy. The Food and Drug Administration places ketoconazole, itraconazole, and fluconazole in category C (studies in animals have shown adverse effects on the fetus, but no adequate studies have been

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performed in humans). Amphotericin B, in contrast, is in category B (no adverse effects on the fetus in animal studies; no adequate studies in humans).

In studies in rats and mice, itraconazole caused dose-related maternal toxicity, embryotoxicity, and teratogenicity at doses of 40 to 160 mg/kg/day. Therefore, it should be used in pregnancy only when its benefits outweigh its potential risks.[55]

DRUG INTERACTIONS

Fluconazole and itraconazole have fewer drug interactions than does ketoconazole, because they are more selective for fungal than for human cytochrome P450 (**TABLE 3**).

Azole agents can increase the concentration of phenytoin, cisapride, oral glucose-lowering agents, warfarin, digoxin, terfenadine, astemizole, and cyclosporine, potentially leading to toxicity.[64] Giving terfenadine or astemizole with itraconazole or ketoconazole is contraindicated because of the potential for serious cardiovascular adverse events, including ventricular tachycardia, *torsade de pointes*, and sudden death.[2]

Rifampin, isoniazid, phenobarbital, carbamazepine, and phenytoin induce hepatic enzymes and can lower fluconazole or itraconazole concentrations, potentially resulting in treatment failure.[65]

Classic Coca-Cola has been reported to increase the serum concentration of ketoconazole, and is used to counteract ketoconazole's compromised absorption in persons with high gastric pH,[66] and to boost its effect in AIDS patients and bone-marrow transplant recipients.

TABLE 3

DRUG INTERACTIONS OF AZOLE AGENTS

Interaction	Ketoconazole	Fluconazole	Itraconazole
Azole agent *increases* the level or effect of these drugs:	Astemizole (+++) Cisapride (++) Corticosteroids (++) Cyclosporine (++) Oral sulfonylureas (++) Phenytoin (++) Terfenadine (+++) Theophylline (++)	Astemizole (++) Caffeine (+) Cyclosporine (+) Oral sulfonylureas (+) Phenytoin (++) Terfenadine (++) Theophylline (++) Warfarin (++) Zidovudine (+)	Astemizole (+++) Cisapride (++) Cyclosporine (++) Digoxin (+) Oral sulfonylureas (+) Phenytoin (++) Terfenadine (+++) Theophylline (++)
Azole agent *decreases* the level or effect of these drugs:	Theophylline* (++)	—	—
These drugs *increase* the level or effect of the azole agent:	Cimetidine (++) Classic Coca-Cola† (++)	Cimetidine (+)	Cimetidine (++)
These drugs *decrease* the level or effect of the azole agent:	Antacids (++) H2 antagonists (++) Isoniazid (++) Omeprazole (++) Rifabutin (++) Rifampin (++)	Carbamazepine (+) Isoniazid (+) Phenobarbital (+) Phenytoin (+) Rifabutin (+) Rifampin (+)	Antacids (++) Carbamazepine (++) H2 antagonists (++) Isoniazid (++) Omeprazole (++) Phenobarbital (++) Phenytoin (++) Rifabutin (++) Rifampin (++)

*Ketoconazole was reported to possibly alter the absorption of sustained-release theophylline dosage forms without altering the pharmacokinetic profile of theophylline; until additional information is available, patients receiving sustained-release theophylline should be observed for reduced theophylline response during ketoconazole administration[65]

†Classic Coca-Cola has been used to increase the systemic concentration of ketoconazole, especially in patients with high gastric pH (eg, with long-term use of omeprazole)[66]

Scale: + minor interaction; ++ moderate interaction; +++ major interaction

DOSAGE AND FORMULATION

The dosage and duration of antifungal therapy depend on the type of infection, the severity of disease, and the patient's immune status (**TABLE 4**). Ketoconazole and itraconazole are available only in oral form; fluconazole comes in both intravenous and oral forms.

Because fluconazole is mainly excreted by the kidneys, dosage adjustment in patients with renal insufficiency is necessary. Patients with a creatinine clearance less than 50 mL/minute should receive 50% of the normal maintenance dose.

Giving itraconazole via nasogastric tube without clogging the tube is a challenge. Ong and Fobes[67] recommend dissolving itraconazole beads in cranberry juice to avoid this problem.

COST CONSIDERATIONS

Ketoconazole 400 mg costs $2 to $4; an equivalent oral dose of fluconazole costs approximately four times as much, itraconazole costs five times as much, and intravenous fluconazole costs 25 times as much—approximately $100 for a 400-mg bag, wholesale, not counting administration fees.

Since fluconazole has high bioavailability, the same dose can be given orally instead of

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TABLE 4

DOSAGE GUIDELINES FOR AZOLE AGENTS

Agent and infection	Dosage		Duration
Ketoconazole			
Systemic infections (including blastomycosis, histoplasmosis)	200–400 mg daily		Candidiasis: at least 1–2 weeks Other systemic mycoses: 6 months Chronic mucocutaneous candidiasis usually requires maintenance therapy
Recalcitrant dermatophyte infections	200–400 mg daily		4 weeks
Fluconazole			
Oropharyngeal candidiasis	Loading: Maintenance:	200 mg 100 mg daily	14 days
Esophageal candidiasis	Loading: Maintenance:	200 mg 100 mg daily	21 days
Systemic candidiasis	Loading: Maintenance:	400 mg 200 mg daily	28 days
Acute cryptococcal meningitis	Loading: Maintenance:	400 mg 200 mg daily	10–12 weeks after cerebrospinal fluid culture becomes negative
Chronic cryptococcal meningitis	200 mg daily		For life, in patient with HIV infection
Vaginal yeast infection	150 mg		One dose
Prevention of candidiasis in bone marrow transplant patients	400 mg daily		Start several days before the anticipated onset of neutropenia, continue for 7 days after the neutrophil count rises above 1000 cells/mm^3
Itraconazole			
Blastomycosis	200–400 mg daily		Variable
Histoplasmosis	200–400 mg daily		Variable
Aspergillosis	200–400 mg daily		Variable
Life-threatening infections	Loading: Maintenance:	200 mg three times a day for 3 days 200–400 mg daily	At least 3 months and until active fungal infection has resolved

Since fluconazole has high bioavailability, the same dose can be given orally instead of intravenously

intravenously without compromising serum concentrations—at one fifth the cost. At 400 mg/day, switching to oral fluconazole would save $78 per day or $546 per week. At 200 mg/day, the oral form would save $56 per day or $392 per week.

For these reasons, we encourage using oral fluconazole whenever possible. However, while intravenous fluconazole is rarely indicated, it may be appropriate in patients who are sedated or unconscious, cannot tolerate the oral form, have significant nausea and vomiting, or have ileus. ■

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