

New Drug Developments

Voriconazole: A New Triazole Antifungal

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OBJECTIVE: To review the currently available information on the pharmacology, pharmacokinetics, efficacy, adverse effects, drug interactions, and dosage guidelines of voriconazole. Comparative data for voriconazole and other azole antifungal agents are described where available.

DATA SOURCES: A MEDLINE search restricted to English-language articles (1966 to September 1999) was conducted, and an extensive review of journals and meeting abstracts was performed. MeSH headings included itraconazole, fluconazole, voriconazole, UK-109,496, and amphotericin B.

DATA EXTRACTION: The data on pharmacokinetics, adverse effects, and drug interactions were obtained from open-label and controlled studies and case reports. Controlled studies and case reports were evaluated to demonstrate the efficacy of voriconazole in treatment of various fungal infections.

DATA SYNTHESIS: Voriconazole is a derivative of fluconazole that demonstrates enhanced in vitro activity against existent and emerging fungal pathogens. Limited data have revealed a favorable pharmacokinetic and safety profile for the agent. Moreover, select clinical trials and case studies of voriconazole suggest good in vivo efficacy against several fungal pathogens including *Candida*, *Aspergillus*, and *Scedosporium*.

CONCLUSIONS: Voriconazole has shown promise in the treatment of superficial and systemic mycoses. While several unresolved issues remain, voriconazole may be a viable therapeutic alternative for fluconazole-resistant mucocutaneous candidiasis and in cases of mild to moderate systemic mycoses requiring chronic treatment or that are refractory to currently available agents.

KEY WORDS: voriconazole, UK-109,496, triazole, antifungal.

Ann Pharmacother 2000;34:1032-43.

Until the 1940s, relatively few agents were available for the treatment of systemic fungal infections. The development of the polyene antifungals, nystatin in the late 1940s, and the broader spectrum, more effective amphotericin B by the late 1950s represented a major advance in the treatment of fungal infections.^{1,2} Amphotericin B quickly became, and remains, the mainstay of therapy for serious infections caused by a broad spectrum of fungi, including *Aspergillus* spp. and *Candida* spp.³ However, its clinical use is associated with numerous adverse effects related to both the drug (nephrotoxicity) and its administration (fever, rigors, hypotension).⁴ Additionally, mortality associated with systemic fungal infections remains unacceptably high despite the use of amphotericin B.^{5,6}

The search for newer systemic antifungals led to the discovery of the azoles several decades later, with the release of ketoconazole in the early 1980s followed by fluconazole and itraconazole in the early 1990s.⁷ These agents were available in oral formulation and demonstrated a relatively improved safety profile compared with that of amphotericin B. However, this class of agents is subject to a number of limitations, including a fungistatic mechanism of action, cytochrome P450-mediated drug-drug interactions, heterogeneous activity against select species of fungi, and a less than optimal pharmacokinetic profile for select agents.^{4,8-11} Due to the azoles' fungistatic nature, the gold standard for serious systemic infections continues to be amphotericin B; however, a clear role for the azoles has been established in the treatment of mild to moderate and refractory infections.¹¹

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The need for more potent antifungals with increased activity against resistant pathogens, shorter treatment durations, and fewer adverse effects stimulates the drive for continued development of systemic antifungals. Voriconazole (UK-109,496, Pfizer Pharmaceuticals, New York, NY) is the newest azole antifungal agent for the treatment of systemic mycosis. Voriconazole was developed as part of a program designed to enhance the potency and spectrum of activity of fluconazole. Currently both an oral and intravenous formulation are undergoing investigation in Phase III trials. This review discusses various pharmacologic aspects of voriconazole, including the mechanism of action, spectrum of activity, pharmacokinetic profile, clinical efficacy, and adverse effects. A comparison with existing azole antifungals is provided when possible to illustrate the potential role of voriconazole in the clinical setting.

Structure and Mechanism of Action

Voriconazole (2*R*,3*S* 2-[2,4-difluorophenyl]-3-[5-fluoropyrimidine-4-yl]-1-[1,2,4-triazol-1-yl] butan-2-ol) is a triazole antifungal and a second-generation synthetic derivative of fluconazole.¹² As with other members of the azole class, voriconazole exerts its mechanism through inhibition of the cytochrome P450-dependent enzyme 14- α -sterol demethylase, thus inhibiting a critical step in the sterol biosynthesis pathway necessary for the production of a functional fungal membrane as well as sustained growth.¹³ Inhibition of 14- α -sterol demethylase prevents lanosterol demethylation in select yeast and mammalian cells, as is demonstrated with fluconazole; however, voriconazole also inhibits 24-methylene dihydrolanosterol demethylation in certain yeast and filamentous fungi, explaining, in part, why voriconazole is active against molds where fluconazole lacks activity.¹³ In actuality, antifungal activity is most likely a result of multiple effects, including cell growth inhibition, morphologic alterations, cessation of cell division, and inhibition of sterol synthesis.³

Voriconazole varies structurally from fluconazole by the addition of a methyl group to the propyl backbone and by the substitution of a triazole moiety with a fluoropyrimidine group (Figure 1). The impact of these changes on the activity of fluconazole is marked and can be illustrated as follows. Fluconazole demonstrates a weak affinity for the target enzyme (14- α -sterol demethylase) of *Aspergillus fumigatus*, with a concentration required to inhibit 50% of enzyme activity (IC_{50}) of 4.8 μ M.¹² The addition of a methyl group to fluconazole's propyl backbone increased the affinity of the compound for the target enzyme by one order of magnitude (IC_{50} 0.48 μ M). The substitution of a triazole ring with a pyrimidine moiety further increased antifungal potency, and the addition of a fluorine to this ring structure at the 5 position enhanced *in vivo* efficacy. Finally, it was determined that the 2*R*,3*S*- enantiomer was the more active of the diastereomer pair. As a result, the synthesis produced a compound with an IC_{50} of 0.053 μ M that conferred a broader spectrum of activity and greater efficacy compared with the parent compound.

Clinical Mycology

The activity of voriconazole *in vitro* has been evaluated against a number of microorganisms. Although *Aspergillus* spp. and *Candida* spp. have been the most extensively studied, other fungi and yeast have been examined. At the time of writing, no data were available on zygomycete or dermatophyte species. Minimum inhibitory concentrations (MICs) for various fungal organisms are provided in Table 1 and discussed below.¹³⁻²⁶

It should be noted that assays used to determine the MIC of a given drug for filamentous fungi are currently not standardized and may vary among and within laboratories.^{27,28} The National Committee for Clinical Laboratory Standards has established guidelines²⁹ for the determination of MIC in select yeast (Table 2).^{8,9,25,30-42} These values, when determined reliably, may be quite useful when dealing with bloodstream infections or when achievable tissue

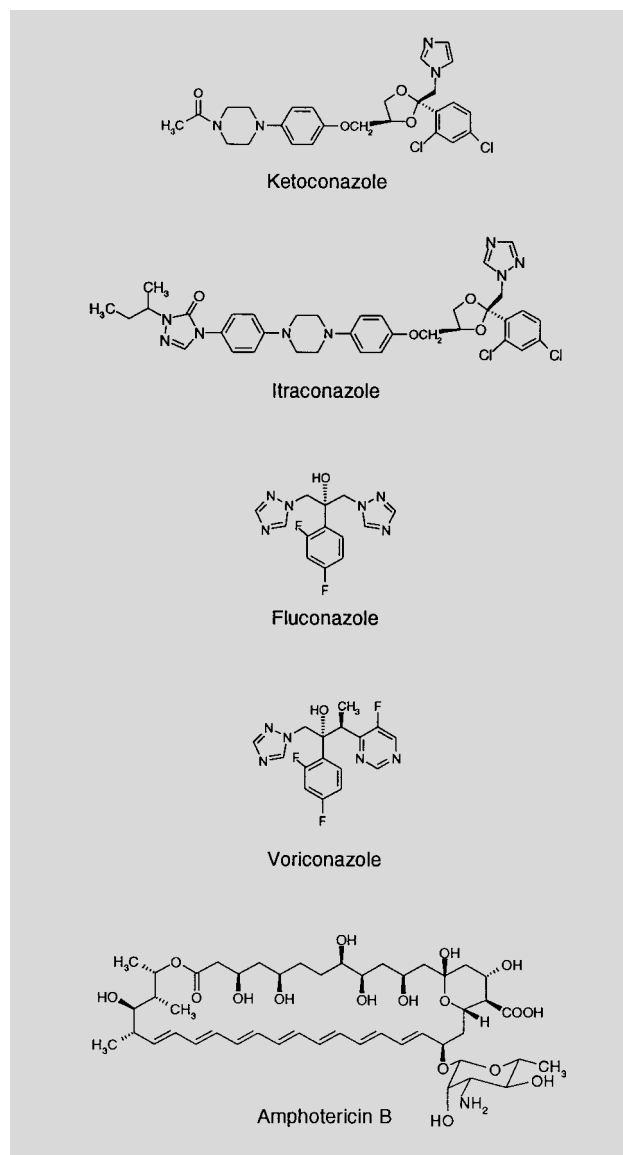


Figure 1. Graphic structures of several antifungals.

concentrations of the drug are available for comparison.^{43,44} However, the applicability of these data becomes more difficult to interpret in the presence of infections at relatively sequestered sites. Additionally, physicochemical and pharmacokinetic data such as formulation, degree of protein binding, lipophilicity, and degree of ionization must be considered under these conditions, as they will affect distribution of the agent in question.

CANDIDA

Voriconazole demonstrates excellent activity against *Candida* spp., with MICs typically <0.125 mg/L.²³ In vitro studies^{16-18,45-47} evaluating the sensitivity of select *Candida* spp. suggest that voriconazole is roughly four to 16 times more active than fluconazole and is roughly comparable to itraconazole. In addition, voriconazole demonstrates MICs that are two to six times lower than those of amphotericin B.

In both *Candida albicans* and *Candida krusei*, ergosterol is the major sterol component of the cell wall, repre-

senting >50% of total sterol content; however, other sterols are present, including obtusifoliol, lanosterol, calciferol, and squalene.¹³ Treatment of fluconazole-susceptible *C. albicans* (MIC necessary to inhibit 80% of pathogens [MIC₈₀] to fluconazole 0.25 mg/L) with voriconazole resulted in a trend toward a smaller mean total sterol content when compared with fluconazole and control. Even in fluconazole-resistant isolates (MIC₈₀ to fluconazole >64 mg/L), voriconazole exposure reduced mean sterol content in a comparable fashion. In contrast, voriconazole appeared to have less of an effect on total sterol content in *C. krusei*. The less marked change on total sterol content observed with fluconazole as compared with voriconazole may be explained in part through examination of changes in specific sterol patterns. In voriconazole-treated *C. albicans*, complete inhibition of ergosterol and obtusifoliol occurred with marked accumulation of precursor sterols. By comparison, fluconazole-treated *C. albicans* demonstrated partial inhibition of ergosterol synthesis and complete inhibition of obtusifoliol with less accumulation of precursor sterols. Similarly, the lack of inhibition of ergosterol and minimal accumulation of precursor sterols in fluconazole-exposed *C. krusei* may provide an explanation as to why it demonstrates MICs >16 mg/L for this organism.

The influence of voriconazole-induced changes in sterol content can be translated into changes observed in fungal cell-wall morphology. At voriconazole's MIC for *C. albicans*, the fungal cells swell and cytoplasmic protrusions can be noted. Although some cells still bud, cell division is halted. Despite these morphologic changes, no leakage occurs, resulting in fungistatic activity.^{3,16} As with *C. albicans*, voriconazole-treated *C. krusei* display separation of the outer envelope and a thinning of the cell wall with some membrane degradation. These same morphologic changes are not apparent in fluconazole-treated *C. krusei*.¹⁶

An additional, although less well-recognized, effect of antifungals involves their ability to impair candidal binding to endothelial and epithelial cells, even at subtherapeutic concentrations.⁴⁸⁻⁵⁰ The ability of the organism to adhere to the host and subsequently penetrate the endothelial barrier is critical to its virulence, allowing subsequent dissemination and systemic infection. In vitro evaluations⁵¹ were conducted to determine the effect of voriconazole on yeast-host cell interactions, specifically fungal adherence and penetration. Vascular endothelial cells were incubated in culture with voriconazole or fluconazole at two times the MIC₈₀ and isolates of fluconazole-sensitive and fluconazole-resistant *C. albicans*. Compared with control cultures, voriconazole significantly ($p < 0.001$) reduced adherence of the fluconazole-sensitive organisms to the en-

Table 1. Comparative MIC Data for Select Organisms Against the Triazole Antifungals and Amphotericin B.^{13-26,a}

Organism	Voriconazole	Itraconazole	Fluconazole	Amphotericin B
<i>Aspergillus flavus</i>	0.25–1	0.25–0.5		0.5–8.0
<i>Aspergillus fumigatus</i>	0.5–1	0.25–0.5		0.5–1.0
<i>Aspergillus niger</i>	0.25–2.0	0.25–4.0		1.0–4.0
<i>Aspergillus ustus</i>	4–8	2–4		2
<i>Blastomyces dermatitidis</i>	<0.03–1 ^b	<0.03–1 ^b	1–64 ^b	<0.03–1 ^b
<i>Candida albicans</i>	<0.03–>4	0.06–0.125	0.25–16	1
<i>Candida glabrata</i>	0.016–0.5	0.5	>8	0.5
<i>Candida krusei</i>	0.125–0.5		>16	
<i>Candida lusitanae</i>	<0.008–0.5	0.125	0.5	0.5
<i>Candida parapsilosis</i>	<0.008–0.25	0.125	0.5–2.0	0.5
<i>Candida tropicalis</i>	<0.008–0.25	0.25	0.29–0.5	0.5
<i>Coccidioides immitis</i>	0.03–0.125 ^b	0.125–2 ^b	2–64 ^b	0.125–1 ^b
<i>Cryptococcus neoformans</i>	<0.03–0.06 ^c	0.25 ^c	4 ^c	1 ^c
<i>Fusarium</i> spp.	0.25–2.0 ^{b,c}			0.5–2.0 ^{b,c}
<i>Histoplasma capsulatum</i>	<0.03–1 ^b	0.03–8 ^b	<0.125–64 ^b	<0.03–2 ^b
<i>Pseudallescherii boydii</i>	<0.06–1.0 ^b	1–4 ^b	4–64 ^b	2–>16 ^b
<i>Scedosporium apiospermum</i>	0.25–0.5 ^d	0.25 ^d	32 ^d	4 ^d

MIC = minimum inhibitory concentration.

^aData determined from National Committee for Clinical Laboratory Standards (NCCLS) microdilutional method and represent MIC₈₀, unless otherwise noted.

^bData determined from NCCLS macrodilutional method.

^cData represent MIC₅₀.

^dData represent MIC₇₀.

endothelial cell surface (~40%). Fluconazole similarly reduced cell surface adhesion compared with control, although to a lesser extent (~20%). No significant reduction in endothelial cell adherence was observed for either agent with fluconazole-resistant strains of *C. albicans*.

Interaction was further defined by assessing the degree of endothelial cell injury caused by these organisms in the presence and absence of the antifungals. Fluconazole-resistant and fluconazole-sensitive *C. albicans* organisms were incubated with voriconazole or fluconazole at 0, 1, 1.5, and 2 times the MIC₈₀ prior to endothelial cell infection. Endothelial cells were infected with 2×10^5 organisms for three hours; cellular damage was assessed by measuring the release of radiolabeled chromium previously incorporated into the endothelial cells. Both fluconazole and voriconazole reduced *C. albicans*-mediated cellular injury in a dose-dependent fashion, with maximal inhibition at two times the MIC₈₀ of 65% and 99%, respectively, when compared with control. The agents had a similar protective effect with fluconazole-resistant organisms, although less marked, demonstrating a reduction by 40% and 90% for fluconazole and voriconazole, respectively.⁵¹

In addition to fungal virulence factors, the competence of the human immune system plays an integral role in the initiation and progression of microbial infections. The immune system works in concert with concurrently administered antifungal agents to impact disease by processes involving pathogen recognition, immune signaling, and, ultimately, eradication of the fungus. For individuals with impaired immunity secondary to disease or drug therapy, combination therapy with colony-stimulating factors (CSFs) has been proposed.⁵² Successful application of CSFs has

been demonstrated in preclinical animal models and select clinical investigations⁵²⁻⁵⁴; however, definitive evidence for the therapeutic and cost-effective potential of these agents in humans remains forthcoming.

These effects were examined by a unique in vitro study⁵⁵ evaluating the activity of voriconazole and fluconazole against *C. albicans* in the presence of immune effector cells with and without CSFs. Fluconazole-sensitive and fluconazole-resistant isolates of *C. albicans* were coincubated with drug alone, effector cell alone (polymorphonuclear cells [PMNs] or peripheral blood mononuclear cells [PBMCs]), or a combination of the two in the presence and absence of CSFs, and the effect on fungal growth was evaluated.

Both fluconazole 1 mg/L and voriconazole 0.1 mg/L were fungistatic, inhibiting growth by comparable activity, but demonstrated a tenfold difference in potency. Inhibition of the growth of fluconazole-resistant isolates of *C. albicans* occurred to a lesser extent despite the presence of significantly higher concentrations of the antifungal agents (voriconazole 62% at 1 mg/L, fluconazole 68% at 20 mg/L). Regardless of CSF stimulation, effector cells demonstrated 100% fungistatic activity. However, when effector cells were combined with antifungals, the combination was fungicidal. Voriconazole 0.1 mg/L demonstrated a 67% increase in killing when combined with PMNs. Fluconazole activity was comparable but, again, demonstrated a tenfold difference in potency. It is worth noting that an increase in voriconazole concentration to 0.1 mg/L did not result in any significant increases in fungicidal activity demonstrated with concurrent incubation of filgrastim (G-CSF)- and regramostim (GM-CSF)-stimulated effector cells.⁵⁵

Table 2. Comparative Data for Members of the Triazole Antifungal Class.^{8,9,25,30-42}

Parameter	Voriconazole	Itraconazole	Fluconazole
Trade name (company)	(Pfizer)	Sporanox (Janssen)	Diflucan (Pfizer)
Formulations	oral (under investigation) intravenous (under investigation)	oral (capsule, solution) intravenous	oral (suspension, tablet) intravenous
Steady-state plasma concentrations (mg/L)	2.1–4.8 (200 mg po bid)	1.1–2 ^a (200 mg qd)	5.6–9.6 (200 mg qd)
t _{max} (h)	<2	3–4	1–3
Oral bioavailability (%)	90	55 ^a	93 ^b
Elimination half-life (h)	6	24 ± 9	31 ± 5
Protein binding (%)	51–67	99.8	11–12
Volume of distribution (L/kg)	2	10–11 ^c	0.7–1.2 ^c
Primary route of elimination	hepatic metabolism	hepatic metabolism	renal excretion
Clearance (L/h)		39.6	1.1 ± 0.5 ^d
NCCLS breakpoints (mg/L) ^e			
susceptible	not established	<0.125	<8
susceptible–dose dependent	not established	0.25–0.5	16–32
resistant	not established	>1	>64

NCCLS = National Committee for Clinical Laboratory Standards; t_{max} = time to reach maximum concentration.

^aVariability is a function of prandial state (absorption of capsule is pH dependent, improved with meals) and oral formulation (e.g., capsule vs. solution).

^bRelative bioavailability.

^cApparent volume of distribution.

^dApparent oral clearance.

^eBreakpoints are validated in *Candida* spp. only.

ASPERGILLUS

As described above, voriconazole demonstrates exquisite affinity for the 14- α -sterol demethylase of *Aspergillus* when compared with fluconazole. MICs for voriconazole against 62 clinical isolates of *Aspergillus* spp. obtained from both immunocompromised and nonneutropenic hosts are comparable to those of itraconazole and amphotericin B.⁵⁶ Voriconazole's fungicidal activity against *Aspergillus* spp. is demonstrated in 86% of isolates with the minimum lethal concentrations ≤ 4 mg/L.¹⁹

As with *Candida*, an element of infection with *Aspergillus* spp. involves tissue penetration, primarily cells of the lung. In a study⁵⁷ designed to assess the ability of voriconazole to protect human pneumocytes from invasion by *A. fumigatus*, cultured A549 pneumocytes were incubated in the presence or absence of voriconazole (8 mg/L) for 16 hours and then thoroughly washed to remove extracellular drug. Resting conidia (25:1 conidia to pneumocyte) were added, subsequently washed, and the rate of attachment (attachment index) was quantified. As was observed with *Candida* spp., the presence of voriconazole significantly ($p < 0.05$) reduced conidial attachment, with an attachment index of $21\% \pm 3\%$, compared with $70\% \pm 7\%$ in the absence of drug.

As discussed above, fungal eradication does not only rely on antifungal activity, but also select aspects of the human immune system. A similar study⁵⁸ explored the use of G-CSF- and GM-CSF-stimulated immune effector cells in combination with antifungals to enhance eradication of *A. fumigatus*, using a study design comparable to that observed in the *Candida* study.⁵⁵ Briefly, the study⁵⁸ included effector cells (PMN and PBMC), the antifungals voriconazole and amphotericin B, and the CSFs G-CSF and GM-CSF. Hyphal growth or inhibition thereof was determined through colorimetric assays using methylthiazole tetrazolium bromide and methoxytetrazolium carboxanilide as markers of cell viability. Conidial germination was completely inhibited for both voriconazole (0.6–5.0 mg/L) and amphotericin B (0.4–5.0 mg/L). For organisms that successfully germinated, inhibition of hyphal growth in the presence of effector cells combined with voriconazole was increased 45% over effector cells alone. Amphotericin B combined with the same effector cells did not result in increased inhibition of hyphal growth, likely due to the fungicidal nature of amphotericin B. Finally, colony-factor stimulation of effector cells in combination with voriconazole further increased inhibition of hyphal growth to 89% and 83% for G-CSF and GM-CSF, respectively.

OTHER FUNGI

Voriconazole may prove to be active in opportunistic infections caused by fungal species other than *Aspergillus* and *Candida*.⁵⁹ Voriconazole is significantly more active than is itraconazole against select *Fusarium* spp.^{60,61} Voriconazole appears to be as active as amphotericin B against *Fusarium* spp. in vitro; however, 82% of *Fusarium* spp. in

one study⁶⁰ demonstrated MICs to amphotericin B of ≥ 1 mg/L compared with voriconazole, where all isolates demonstrated an MIC < 2 mg/L.

Voriconazole appears to be at least 10 times more potent than fluconazole against clinical isolates of *Cryptococcus neoformans*.⁶² Fluconazole demonstrated MICs ≤ 8 mg/L for 82% of the isolates and 16–32 mg/L for 14% of the isolates.⁶³ In contrast, voriconazole and itraconazole demonstrated MICs ≤ 0.5 mg/L for 100% of the isolates. Voriconazole appears to be more active than itraconazole, with MICs approximately 25–50% below those of itraconazole. Against *C. neoformans* (fluconazole MICs > 64 mg/L), voriconazole and itraconazole both demonstrate MICs in the range of 1–2 mg/L. The increase in fluconazole MIC of these isolates resulted in a parallel increase in itraconazole and voriconazole MIC, suggesting cross resistance between the azoles. As discussed above, the pharmacokinetic profile of the respective drugs will dictate their clinical utility in clinical situations where MICs approach achievable serum concentrations.

An in vitro study⁶⁴ of 19 fungal species including *Candida* spp., *Blastomyces* spp., *Cryptococcus* spp., *Hansenula anomala*, *Rhodotorula rubra*, *Saccharomyces cerevisiae*, *Sporobolomyces salmonicolor*, and *Trichosporon beigellii* compared the activity of voriconazole to fluconazole, itraconazole, and amphotericin B. The activity of voriconazole exceeded that of fluconazole and was comparable to that of itraconazole. Exceptions included a single isolate of *Candida tropicalis* that demonstrated an MIC > 16 mg/L for all antifungals tested and several isolates of *R. rubra* for which the MIC of voriconazole exceeded those of amphotericin B and itraconazole. Voriconazole demonstrates MICs comparable to those of amphotericin B against *Exophiala spinifera*,⁶⁵ but its MICs are lower than those of itraconazole and amphotericin B against *Sporothrix schenckii* and *Paecilomyces variotti*. Other fungi highly susceptible to voriconazole include *Blastomyces dermatitidis*. Voriconazole is superior to itraconazole against *Acremonium kiliense*, *Lasiodiplodia theobromae*, *Scedosporium proliferans*, and *Scopulariopsis brevicaulis*.⁶¹

Pharmacokinetics

Limited data are currently available on the pharmacokinetics of voriconazole in humans; however, data available to date are summarized below and in Table 2.^{8,9,25,30–42}

ABSORPTION

Voriconazole is well absorbed following oral administration, with a bioavailability of 90% and maximum plasma concentrations achieved within two hours of oral administration of the agent.³³ The drug exhibits nonlinear pharmacokinetics, quite possibly due to saturable first-pass metabolism. Achievable steady-state concentrations following oral administration (200 mg bid) have ranged from 2.1 to 4.8 mg/L and 1.4 to 1.8 mg/L for peak and trough concentrations, respectively.³⁴ No data are currently avail-

able reporting the influence of meals and/or their constituents on the absorption of orally administered voriconazole.

DISTRIBUTION

Voriconazole is distributed widely in humans, with a steady-state volume of distribution of 2 L/kg.³³ Voriconazole is moderately bound to plasma proteins (51–67%), as reflected by saliva concentrations approximately 65% of those in plasma; however, specific plasma proteins to which the agent is bound have yet to be elucidated. Limited data are available on voriconazole distribution in extravascular tissue. A single report⁶⁶ suggests that voriconazole distributes into the cerebrospinal fluid at concentrations of those in serum. Specific voriconazole concentrations (900 mg iv qd × 1, then 450 mg iv qd) measured in an individual with central nervous system aspergillosis demonstrated cerebrospinal fluid concentrations between 1.36 and 2.65 mg/L, with concurrent plasma concentrations between 3.31 and 3.9 mg/L.

METABOLISM

Voriconazole undergoes extensive hepatic metabolism via the cytochrome P450 enzymes, primarily CYP2C9 and CYP3A4. To date, eight metabolites have been characterized, of which three are major metabolites and five are minor metabolites.³⁵

ELIMINATION

Voriconazole demonstrates an elimination half-life of approximately six hours.³³ However, in patients receiving extended courses of therapy, six days are required to recover 90% of the drug in urine and feces.^{33,35} The metabolites of voriconazole are primarily eliminated via urinary excretion; however, the time course for their elimination has yet to be defined. Less than 5% of parent compound has been detected in the urine.³⁵

SPECIAL POPULATIONS

To date, no formal evaluations are available addressing the pharmacokinetics of voriconazole in the elderly or children. However, two case reports determined steady-state voriconazole concentrations in children. An eight-year-old boy⁶⁷ receiving oral voriconazole 10 mg/kg/d for the treatment of invasive pulmonary scedosporiosis demonstrated peak and trough serum concentrations of 5 and 0.54 mg/L, respectively. In the other report,⁶⁸ a five-year-old child receiving oral voriconazole 7 mg/kg/d for the treatment of invasive aspergillosis demonstrated peak and trough concentrations between 3–4.5 mg/L and ≤2 mg/L, respectively. Intravenous therapy in this child achieved maximal peak and trough values of approximately 6 and 3 mg/L, respectively, at doses between 7 and 9 mg/kg/dose, twice daily.

Therapeutic Use

CANDIDIASIS

Candida spp. are the leading cause of nosocomial fungal infections, with the principal species being *C. albicans*; however, infections with nonalbicans species continue to rise. In addition, *C. albicans* is the fourth most prevalent isolate of all nosocomial blood stream infections, accounting for 8–11% of total isolates.¹¹ Fluconazole remains the drug of choice for superficial and mild to moderate systemic infections, while amphotericin B remains the gold standard for serious systemic *Candida* infections.⁶⁹

In addition to the prevalence of infections with *Candida* spp., resistance among these isolates is becoming an increasing threat to those with systemic mycoses. In HIV-infected individuals receiving fluconazole prophylaxis, up to 33% of *C. albicans* strains demonstrate resistance.³ Moreover, prophylaxis contributes to an increase in non-*C. albicans* colonization, of which select species may demonstrate marked resistance to currently available agents.^{3,70}

Scant data are available on the in vivo efficacy of voriconazole in the treatment of *Candida* infections. Although animal models of systemic candidiasis appear to suggest similar efficacy between voriconazole and the currently available triazoles, reports of response observed with this agent in humans is limited to a single abstract⁷¹ and a small trial,³⁴ both designed to evaluate efficacy in mucocutaneous infection. In a Phase II trial⁷¹ comparing three doses of voriconazole (50 mg qd, 200 mg qd, 200 mg bid × 7 d) for the treatment of HIV-infected individuals with oropharyngeal candidiasis, doses of 200 mg once or twice daily achieved a clinical efficacy rate between 80% and 100%. Although data on median CD4+ cell counts (50–60 cells/mm³) are available for these subjects, no additional data, including the number of patients evaluated, median age of patients, history of previous treatment, and prophylaxis for the condition, are described in the report.

Another trial³⁴ evaluated the efficacy of voriconazole in the treatment of fluconazole-resistant oroesophageal candidiasis. Twelve HIV-positive patients (age 26–69 y) with advanced HIV infection (CD4+ cell count range 1–20 cells/mm³) and endoscopically confirmed oroesophageal candidiasis refractory to fluconazole were enrolled. All subjects demonstrated infection by *C. albicans*, with the exception of a mixed infection (*C. albicans* and *Candida glabrata*) in a single individual. Treatment was initiated with oral voriconazole 200 mg twice daily, and efficacy was assessed on day 7 and weekly thereafter for the duration of the study. Favorable clinical response was defined by sum of complete and partial responders (significant improvement), and mycologic response was defined by disappearance of organism on culture. Ten patients (83%) responded positively to therapy: six patients with a complete clinical response at seven days, three patients markedly improved at seven days, and one patient with a complete clinical response at 14 days. The remaining two patients were unchanged clinically on follow-up evaluation. The overall duration of clinical response was highly variable,

persisting between one and 40 weeks. Mycologic eradication was observed in fewer subjects (42%) by day 7, lasting between two and 14 weeks.

Based on currently available data, voriconazole appears to achieve therapeutic salivary concentrations and, thus, not surprisingly demonstrates very good response in the treatment of oropharyngeal candidiasis.^{33,34,71} Although response rates for the existing antifungal agents may vary as a function of underlying disease severity, reports⁷²⁻⁷⁵ typically suggest clinical response rates for currently administered azole antifungals in excess of 75% for individuals infected with HIV. Given the above clinical response rates between 80% and 100% for voriconazole and a lack of information detailing specifics, at best one can conclude that voriconazole is at least equally effective as the current first-line agents.

ASPERGILLOSIS

Aspergillus spp. are a ubiquitous group of fungi found in soil and other organic material. Infection typically occurs as a result of inhalation of airborne conidia, which can result in lung or sinus infection and subsequently invade adjacent blood vessels to cause disseminated disease.⁷⁶ Any of a number of species can cause infection; however, infection is most commonly observed with *A. fumigatus* (>80%) followed distantly by *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*.⁶⁵ Current treatment includes resection and antifungal therapy, typically with amphotericin B as the first-line agent.^{3,11}

Despite antifungal therapy, morbidity and mortality with aspergillosis remain high.⁷⁷ Mortality in invasive pulmonary aspergillosis is between 50% and 90% despite antifungal treatment. Immunocompromised patients are particularly at risk, with mortality in chemotherapy-induced neutropenic patients as high as 50–60% and mortality rates in bone marrow transplant patients as high as 90%.¹⁰ Moreover, mortality observed with central nervous system infections approaches close to 100% despite treatment with antifungals.⁶⁶

A number of small studies have evaluated the role of voriconazole in the treatment of systemic *Aspergillus* infections. An open-label study⁷⁸ evaluated the role of orally administered voriconazole 200 mg twice daily for the management of invasive aspergillosis in nonneutropenic patients, approximately 50% of whom had failed previous therapy with itraconazole or amphotericin B. Of 25 patients enrolled in the study, data were available on 13 patients at the time of interim analysis. At the completion of therapy (median 12 wk), an overall favorable response rate of 69% was observed: two subjects demonstrated a complete response and seven a partial response. The remaining four subjects (31%) failed treatment; however, specific data on these failures were not detailed. Additional data (e.g., site of infection, median age of patients, history of underlying disease, duration of previous treatment) are not provided for the subjects of this study, making data interpretation of these results difficult.

An additional open-label study⁷⁹ evaluated the efficacy of voriconazole for the treatment of acute invasive aspergillosis in 71 immunocompromised patients. The regimen used a loading-dose regimen of 6 mg/kg every 12 hours intravenously for two doses, followed by 3 mg/kg every 12 hours intravenously for six to 27 days, and then 200 mg orally twice daily for a total duration of four to 24 weeks. As above, the reported data represent those from an interim analysis with 36 of 71 patients evaluated for the report. A favorable response, defined as complete or partial response, was seen in 27 of 36 subjects (75%), with the remaining 25% demonstrating stable disease or therapeutic failure. Of the subjects enrolled, 72% had failed prior treatment with itraconazole or amphotericin B.

A study⁸⁰ designed to evaluate the impact of early diagnosis with thoracic computed tomography (CT) scan and surgery on the outcome of invasive pulmonary aspergillosis in neutropenic patients provided limited data on response rates for select antifungals including amphotericin, flucytosine, itraconazole, and voriconazole. The study population was infected with various species of *Aspergillus*, including *A. fumigatus*, *A. flavus*, and *Aspergillus nidulans*. Of 36 patients enrolled in this evaluation, four received voriconazole (median dose 6 mg/kg/d, median duration 63 d), with successful treatment in three patients (75%) and one failure in a patient who subsequently responded to treatment with itraconazole.

In addition to the few clinical trials detailing voriconazole's efficacy in the treatment of aspergillosis, select case reports are available detailing the efficacy of voriconazole in the treatment of systemic infections with *Aspergillus* spp., including infections in the lungs, sinuses, bones, and central nervous system. A case report⁷⁶ details treatment in a 37-year-old immunocompetent woman with invasive sinusitis (*A. fumigatus* and *Proteus* spp.) involving the ethmoid, maxillary, and sphenoid sinuses. Therapy was initiated with itraconazole 100 mg/d, but infection persisted and progressed to subsequent otitis and osteitis despite two courses of itraconazole (100 mg/d, but then increased to 400 mg/d after 5 mo) over more than five months. Persistent symptoms prompted the switch to voriconazole (200 mg twice daily × 14 mo), to which the patient demonstrated marked clinical improvement. No clinical or radiologic evidence of residual infection was present at the time of the report five years after the discontinuation of voriconazole therapy.

A second case report⁶⁶ details the efficacy of voriconazole for refractory aspergillosis (species not identified) in an 18-year-old man with acute lymphoblastic leukemia. The patient developed clinical symptoms of fever and pleural chest pain shortly after initiation of his chemotherapy protocol, and antifungal therapy was initiated with amphotericin B. Therapy was subsequently switched to liposomal amphotericin B and, with the development of meningismus, switched again to a regimen of intrathecal amphotericin B in combination with itraconazole. Evidence of disease progression despite therapy prompted a final switch to voriconazole, with a loading dose of 900

mg intravenously on day 1, followed by 450 mg intravenously daily for six days and then 200 mg orally twice daily for just under six months. Evidence of infection resolved in this patient; however, the patient subsequently died due to refractory leukemia.

A final case report⁸¹ demonstrates response to voriconazole in a 30-year-old man with chronic granulomatous disease and micronodular pulmonary aspergillosis (*A. fumigatus*). Treatment was initiated with voriconazole 200 mg twice daily, and a rapid clinical response was observed, with radiologic abnormalities diminished by two weeks and absent by three months. After a total of nine months of treatment with voriconazole and no further evidence of infection, voriconazole was discontinued and prophylaxis with itraconazole was initiated. At the time of publication, the patient had been symptom free for three years.

Response rates for existing antifungal agents are highly variable and subject to numerous underlying conditions with therapeutic failure. The failure is highest in cases of extrapulmonary infection and in patients with prolonged granulocytopenia and chronic immunodeficiency conditions; subsequently, response rates rarely exceed 65%.⁸² Larger trials⁸²⁻⁸⁷ report clinical improvement of 40–60%, 20–80%, and 50–65% following treatment with itraconazole, amphotericin, and lipid-based amphotericin B products, respectively. Voriconazole demonstrated an impressive response rate, with 75% of the subjects in these small trials, a number of whom had failed previous therapy, demonstrating complete or partial resolution of infection. Although information on larger numbers of patients are necessary, currently available data appear to suggest that the efficacy of voriconazole in the treatment of invasive aspergillosis may be comparable and possibly exceed that of currently available agents. Additionally, it may potentially serve an important role in the treatment of infections refractory to current therapy.

OTHER MYCOSES

Limited data are available on the use of voriconazole in fungal infections other than those noted above. Two case reports of *Scedosporium apiospermum* infection are described below. The first case²⁴ of disseminated *S. apiospermum* involved a 25-year-old man who was immunocompromised secondary to acute myeloid leukemia. While receiving chemotherapy, the patient developed profound granulocytopenia with persistent fever despite antibiotic therapy. Antifungal therapy with amphotericin B lipid complex was initiated, with no observable improvement. The organism was subsequently identified and sensitivities performed, with resultant MICs for itraconazole, voriconazole, ketoconazole, miconazole, amphotericin, fluconazole, and flucytosine of 0.25, 0.25, 1, 2, 4, 32, and >64 mg/L, respectively. Therapy was initiated with voriconazole (400 mg every 12 h × 2 doses, then 200 mg every 12 h), and significant clinical improvement and defervescence was observed within a few days despite persistent neutropenia. The patient's skin lesion continued to improve,

and he remained afebrile while taking voriconazole; however, he eventually died for reasons unrelated to fungal infection or voriconazole administration.

A second case report⁶⁷ details the use of voriconazole for the treatment of invasive pulmonary scedosporiosis (*S. apiospermum*). An eight-year-old boy with chronic granulomatous disease was admitted to a hospital for fever, cough, and tachypnea. A chest X-ray and CT scan revealed a pulmonary abscess in the left lower lobe; therapy with intravenous amphotericin B and flucytosine was initiated for presumptive pulmonary aspergillosis. With the apparent absence of improvement following one month of therapy, a CT scan was repeated, demonstrating evidence of extension into chest wall with pleural and costal involvement. Cultures from both sputum and biopsy specimens were positive for *S. apiospermum*, and resultant determinations of MIC-yielded values for miconazole, voriconazole, itraconazole, amphotericin B, and flucytosine of 0.3, 0.4, 0.7, 8, and 12 mg/L, respectively. Therapy was initiated with miconazole but was subsequently discontinued due to anaphylaxis. Therapy was also attempted with itraconazole, but since there was no symptomatic improvement after two weeks, the patient was switched to oral voriconazole 10 mg/kg/d plus subcutaneous interferon gamma. The child demonstrated significant improvement by two months of treatment, with serum titers negative by four months. The persistence of residual infiltrate at seven months prompted a thoracotomy, with resultant biopsy specimens positive on histology for fungal elements but negative on culture. Treatment was continued for an additional eight months, without any new lesions recorded on CT scan one year after surgery.

Scedosporiosis is an uncommon infection, with the majority of details surrounding effective treatment limited to case reports. Anecdotal evidence of clinical response to fluconazole, ketoconazole, amphotericin, and flucytosine alone or in combination are available in select case reports.⁸⁸⁻⁹¹ However, a number of case series^{92,93} report extremely poor response rates (10–12%) for invasive scedosporiosis in the immunocompromised host. As with other fungal infections, voriconazole may be an appropriate treatment alternative; however, additional data are needed to define the role of this agent in treatment regimens.

Adverse Effects

The case reports and clinical studies detailed above have described, to a limited extent, adverse events observed with the use of voriconazole. Transient, dose-related visual disturbances (e.g., increased brightness, blurred vision) have been reported^{66,71,78,79} to occur in approximately 8–10% of patients receiving this agent; however, no potential mechanism by which this adverse event occurs has been described. As with the existing azoles, elevations in liver function test results have similarly been observed in patients receiving voriconazole, resulting in the discontinuation of treatment in select cases.^{66,78,79} In addition, one case report⁷⁶ suggests a possible relationship between voriconazole ad-

ministration and the occurrence of photosensitivity, with skin lesions consistent with discoid lupus vulgaris developing under exposure to strong sunlight. Evaluation in larger trials and postmarketing surveillance will be necessary to further outline adverse events that may be expected with the use of this agent.

There is evidence⁹⁴ suggesting that voriconazole may not possess the same ability to alter serum hormone concentrations as is seen with ketoconazole, although this remains to be elucidated *in vivo*. Voriconazole demonstrates a lower affinity for mammalian 14- α -sterol demethylase as compared with ketoconazole and itraconazole, suggesting the potential for a lesser effect on inhibition of mammalian sterol biosynthesis. Ketoconazole appears to be the most potent azole inhibiting mammalian 14- α -sterol demethylase, with an IC₅₀ for voriconazole, itraconazole, and ketoconazole of 8, 2.3, and 1.4 μ M, respectively. This finding reflects a lesser degree of interaction with the cytochrome P450 enzymes responsible for the metabolism of steroid hormones.

Drug Interactions

To date, there is no information on the occurrence of drug–drug interactions with voriconazole, although it would not be unreasonable to suspect potential cytochrome P450–mediated drug interactions secondary to the known mechanism of action for this class of agents. As described above, metabolism of voriconazole proceeds through a number of cytochrome P450 enzymes, of which CYP2C9 and CYP3A4 are likely the most clinically relevant isoforms. Future reports on the affinity of voriconazole for these cytochrome P450 isoforms and inhibitory rate constants will clarify the potential role of voriconazole in inhibiting metabolism of select substrates for these enzymes. Until these data are available, caution is warranted with the coadministration of voriconazole and substrates of the aforementioned cytochrome P450 isoforms, especially those with a relatively narrow therapeutic index. Similarly, drug–food interactions are not described. However, as with existing azoles, one may see a potential interaction with grapefruit juice should CYP3A4 play a significant role in the biotransformation of voriconazole. As above, enzyme rate constants for the various cytochrome P450 isoforms involved in the biodisposition of voriconazole will further clarify these questions.

Areas Where Additional Information Is Needed

The role of voriconazole in the treatment of superficial and systemic mycoses will likely depend on the infecting organism and site of infection. Based on the limited data available for voriconazole, fluconazole will likely remain the gold standard for mild to moderate superficial infections of fluconazole-sensitive *Candida* spp. For fluconazole-resistant isolates, cost and concurrent medication use will dictate the decision between itraconazole and voriconazole given that the adverse event profile of voriconazole remains comparable with that observed currently for

itraconazole. Amphotericin B will remain the first-line agent for serious systemic fungal infections; however, in cases of mild to moderate disease and chronic or refractory infections, voriconazole may play a major role in therapy. The fungicidal activity observed with voriconazole against select clinical isolates provides a distinct advantage over the currently available triazole antifungals; however, additional information (i.e., larger clinical trials, full pharmacokinetic and safety profile) is needed before voriconazole will be considered adequately assessed. The following issues need clarification.

DOSAGE AND ADMINISTRATION

No clear dosing and administration guidelines have been established for voriconazole in fungal mycoses. In two studies of oropharyngeal candidiasis,^{34,71} 200 mg orally twice daily for seven to 14 days has proven to be an effective regimen and will likely constitute an appropriate initial dose for the treatment of such infections. For other systemic mycoses, no single effective regimen has been established based on the currently available studies. Various dosing regimens have been employed, some using a loading dose; however, larger clinical trials and additional efficacy data are necessary to fully establish effective dose regimens.

PRECAUTIONS/CONTRAINDICATIONS

To date, no precautions or contraindications have been established. However, due to evidence of elevations in liver function test results, it may be prudent to use caution in individuals with hepatic impairment. Moreover, caution may be warranted in patients with existing ocular disorders, due to the visual disturbances that have been observed.

PREGNANCY AND LACTATION

No information is yet available on the pregnancy category of voriconazole and the excretion of the parent compound and/or its metabolites into breast milk.

COMMERCIAL AVAILABILITY

Although intravenous and oral formulations of voriconazole have been used in clinical trials, specific information on formulation and dosage strengths that will become available are unknown to date. Additionally, the anticipated cost of voriconazole on release as compared with the existing triazoles has yet to be determined.

CROSS-RESISTANCE

Fungi demonstrate a number of resistance mechanisms against the azoles, including altered cell-wall permeability, altered target enzyme production (i.e., decreased affinity, increased production), upregulation of efflux pumps responsible for extrusion of drug from cell, and an innate ability to survive despite inhibition of sterol biosynthe-

sis.^{70,95-98} Although the emergence of resistance to voriconazole exposure has not yet been systematically evaluated, cross-resistance to existing azoles appears to be present, as evidenced by higher MICs for voriconazole in fluconazole-resistant versus fluconazole-sensitive organisms.¹³ Despite this, the MICs for voriconazole remain lower than the MICs of currently available antifungals and within the range necessary to sufficiently inhibit fungal growth for a number of fungal pathogens.⁵⁹

Summary

The rising incidence of antifungal infections is fueling the drive for more potent antifungals and has resulted in the development of voriconazole, a new triazole antifungal. Voriconazole is a synthetic modification of fluconazole that demonstrates an increased affinity for the enzymes responsible for fungal sterol biosynthesis and in vitro efficacy against several existent and emerging fungal pathogens. Excellent activity against *Candida* spp. has been observed for voriconazole, including alterations in cell-wall morphology, increased potency in combination with immunostimulants, and enhanced protection against endothelial cell damage. Moreover, voriconazole has proven to be a viable therapeutic option in limited case studies and small trials of candidal infections. Exquisite activity has been demonstrated against *Aspergillus* spp., including fungicidal activity, increased potency in combination with immunostimulants, and enhanced protection of host cells against fungal adherence and invasion. Infections with *Aspergillus* spp. have responded favorably to voriconazole administration, potentially providing a therapeutic alternative to existing agents. Limited data suggest that voriconazole demonstrates a favorable pharmacokinetic and safety profile that may be equivalent to the existing triazoles should additional data fall in line with currently available information. While several unresolved issues remain, including cost, extent and significance of drug–drug interactions, cross-resistance, and additional adverse events, voriconazole likely will provide additional advantages to the current armamentarium of antifungal agents.

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EXTRACTO

OBJETIVO: Revisar la información actualmente disponible sobre la farmacología, farmacocinética, eficacia, efectos adversos, interacciones con otros medicamentos, y guías de dosificación de voriconazole. Se presentan también datos que comparan voriconazole con otros antifungales que pertenecen a la misma clasificación.

FUENTES DE DATOS: Se realizó una búsqueda utilizando la base de datos de MEDLINE en el idioma inglés para el período comprendido entre los años 1996 a septiembre de 1999. Además, se revisaron revistas científicas y extractos. Las palabras claves utilizadas son: itraconazole, fluconazole, voriconazole, UK-109,496, y amphotericin-B.

EXTRACCIÓN DE DATOS: Los datos sobre la farmacocinética, efectos adversos, e interacciones de drogas se obtuvieron de estudios abiertos, controlados, e informes de casos. Los estudios controlados e informes de casos fueron evaluados para demostrar la eficacia de voriconazole en el tratamiento de varias infecciones fúngicas.

SÍNTESIS: Voriconazole es un derivado de fluconazole que demuestra actividad in vitro contra patógenos fúngicos existentes y emergentes. Datos limitados revelan una farmacocinética y perfil de seguridad favorables para el agente. Además, algunos estudios clínicos e informes de casos sugieren buena eficacia in vivo contra varios hongos, incluyendo *Candida*, *Aspergillus* y *Scedosporium*.

CONCLUSIONES: Voriconazole parece ser prometedor en el tratamiento de micosis superficial. Voriconazole también parece ser una alternativa terapéutica para candidiasis mucocutánea resistente a fluconazole y en el tratamiento de casos leves a moderados de micosis sistémica que requiere tratamiento crónico o que son refractarios a otros agentes.

Wanda Maldonado

RÉSUMÉ

OBJECTIF: L'objectif de cette publication est de revoir l'information disponible actuellement sur la pharmacologie, la pharmacocinétique, l'efficacité, les réactions adverses, les interactions médicamenteuses, et les recommandations posologiques du voriconazole. Des données comparant le voriconazole aux autres antifongiques sont décrites lorsque disponibles.

REVUE DE LITTÉRATURE: Une recherche automatisée de la banque de données MEDLINE a été effectuée pour identifier les publications de langue anglaise parues depuis 1966 jusqu'à septembre 1999. De plus, les compte rendus et résumés de communication lors de réunions d'envergure ont été revus de façon extensive. Les mots clés incluaient: itraconazole, fluconazole, voriconazole, UK-109,496, et amphotéricine B.

EXTRACTION DES DONNÉES: Les données sur la pharmacocinétique, les réactions adverses, et les interactions médicamenteuses ont été obtenues à partir d'études contrôlées ou non et des rapports de cas. Les études contrôlées et les rapports de cas furent utilisés pour les données d'efficacité.

RÉSUMÉ: Le voriconazole est un dérivé du fluconazole qui démontre une activité in vitro supérieure contre les pathogènes fongiques existants et ceux d'apparition récente. Un nombre restreint de données accordent à ce produit un profil d'innocuité et une pharmacocinétique favorable. De plus, certaines études et rapports de cas suggèrent une bonne efficacité in vivo contre plusieurs pathogènes fongiques incluant le *Candida*, l'*Aspergillus*, et le *Scedosporium*.

CONCLUSIONS: Le voriconazole semble un agent prometteur dans le traitement de mycoses superficielles et profondes. Bien que plusieurs questions demeurent encore en suspens (i.e., coût, résistance croisée, interactions médicamenteuses, réactions adverses), le voriconazole pourrait être une alternative thérapeutique acceptable lors de candidoses muco-cutanées résistantes au fluconazole et dans le cas de mycoses systémiques légères à modérées nécessitant un traitement chronique ou encore celles réfractaires aux agents présentement disponibles.

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