Voriconazole: A New Triazole Antifungal Agent

Margaret M Pearson, P David Rogers, John D Cleary, and Stanley W Chapman

OBJECTIVE: To review the pharmacology, in vitro susceptibility, pharmacokinetics, clinical efficacy, and adverse effects of voriconazole, a triazole antifungal agent.

DATA SOURCES: A MEDLINE search, restricted to English language, was conducted from 1990 to June 2002. Supplementary sources included program abstracts from the Interscience Conference on Antimicrobial Agents and Chemotherapy and the Infectious Diseases Society of America from 1996 to 2001 and manufacturer information available through the Food and Drug Administration's Web site.

DATA EXTRACTION: All published and unpublished trials and abstracts citing voriconazole were selected.

DATA SYNTHESIS: Voriconazole has shown in vitro activity against many yeasts and a variety of mold and dermatophyte isolates. Voriconazole can be administered either orally or parenterally. It exhibits good oral bioavailability, wide tissue distribution including distribution into the central nervous system, and hepatic metabolism. Drug interactions occur through inhibition of the CYP2C9, CYP2C19, and CYP3A4 isoenzymes, resulting in alterations in kinetic parameters of either voriconazole or the interacting agent. Efficacy has been illustrated in open, noncomparative studies of aspergillosis in immunocompromised patients. Human case reports describe successful treatment of rare fungal pathogens. The most commonly reported adverse events include visual disturbances and elevations in liver function tests.

CONCLUSIONS: Voriconazole is at least as effective as amphotericin B in the treatment of acute invasive aspergillosis in immunocompromised patients. It has similar efficacy as fluconazole in treatment of esophageal candidiasis. Voriconazole did not achieve statistical non-inferiority to liposomal amphotericin B for empirical therapy in patients with neutropenia and persistent fever, diminishing enthusiasm for use in this indication until additional trials are completed. Based on case reports and in vitro efficacy, voriconazole may prove to be a clinically useful agent in the treatment of other fungal disease.

KEY WORDS: antifungal, voriconazole.

Ann Pharmacother 2003;37:420-32.

Published Online, 9 Feb 2003, *www.theannals.com*, DOI 10.1345/aph.1C261

It is well known that patient populations at risk for serious fungal infection have increased dramatically in recent years. These populations include patients with AIDS, those receiving cancer chemotherapy or organ transplantation, and others receiving immunosuppressive medications on a long-term basis. Additionally, the spectrum of invasive mycoses is changing, with frequency of invasive aspergillosis and the number of infections due to non-albicans *Candida* spp. on the rise.[1] Options available for treatment of invasive mycoses have included amphotericin B and its lipid preparations, the azole antifungals ketoconazole, itraconazole, and fluconazole, and the echinocandin caspofungin. Although it has a broad spectrum of activity, amphotericin B is associated with nephrotoxicity and infusion-related adverse effects. Nephrotoxicity is decreased in patients treated with lipid preparations of amphotericin B, but infusion-related adverse effects may still occur. Limitations for other antifungals include lack of an oral preparation for

Voriconazole (Vfend, Pfizer Pharmaceuticals)

Author information provided at the end of the text.

caspofungin, limited safety information for the cyclodextran intravenous formulation of intraconazole, and the limited spectrum of fluconazole.

The triazole antifungal agent voriconazole is a derivative of fluconazole with improved antifungal activity and enhanced potency against fungal 14α-demethylase[2-5] (Figure 1). Both intravenous and oral formulations have been developed. Voriconazole has been approved by the Food and Drug Administration for treatment of acute invasive aspergillosis and for treatment of serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp. The purpose of this article is to address voriconazole's potential clinical role as an antifungal agent. The pharmacology, pharmacokinetics, and clinical mycology of voriconazole are also presented.

Pharmacology

Azole antifungal agents inhibit fungal cytochrome P450–dependent 14α-sterol demethylase of ergosterol biosynthesis, resulting in depletion of ergosterol and accumulation of 14-methylated sterols. The degree of inhibition of this enzyme system is dose-dependent and variable among the different azole agents.[4,5] This is demonstrated for *Aspergillus fumigatus* for which a greater affinity for the target enzyme, lanosterol 14α-demethylase, results in voriconazole minimum inhibitory concentrations (MICs) tenfold less than fluconazole MICs.[2] Voriconazole is also more effective than fluconazole in inhibiting the14α-demethylase of *Candida krusei*, possibly due to contact with a greater number of the enzyme's amino acids.[5]

Voriconazole may possess an additional mechanism of antifungal activity. Transmission electron microscopy demonstrating cell wall thinning and separation in *Candida albicans* and *C. krusei* is consistent with disruption of chitin synthase during antifungal therapy.[6]

In Vitro Antifungal Activity

Voriconazole has shown in vitro activity against many yeasts and a variety of mold and dermatophyte isolates. A summary of in vitro activity is provided in Tables 1[7-23] and 2.[7,9,10,14,24-26] The National Committee for Clinical Laboratory Standards has not assigned breakpoints for voriconazole against fungi, and the relationship between clinical outcome and in vitro susceptibility has yet to be elucidated.[27]

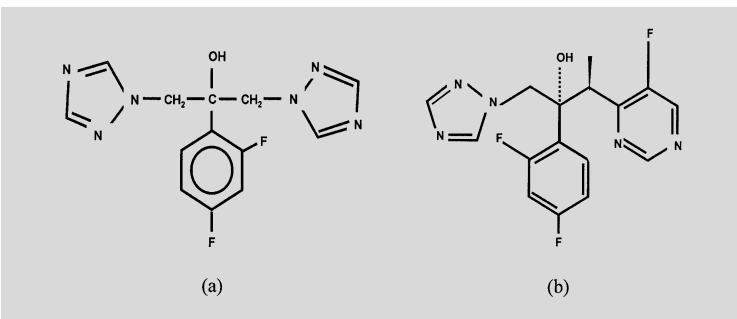

Figure 1. Chemical structure of fluconazole (a) and voriconazole (b).

Aspergillus spp.

Voriconazole MIC ranges for *Aspergillus* spp. are similar to those of itraconazole, and in vitro activity against *A. fumigatus* and *A. flavus* is comparable to that of amphotericin B (Table 1).

Voriconazole is fungicidal against *A. fumigatis* and *A. flavus*. Minimal lethal concentrations (MLCs) range from 0.5–8 μg/mL, with most isolates exhibiting MLCs ≤4 μg/mL.[8,28] Kill curves demonstrate a reduced number of colony-forming units within 24 hours compared with initial inoculum for concentrations of voriconazole ranging from 1.25–10 μg/mL. Voriconazole 5 μg/mL achieved approximately 95% killing of *A. fumigatis*, which was superior to itraconazole (85% killing at 5 μg/mL), but not to amphotericin B (99% killing at 5 μg/mL).[28]

Voriconazole and terbinafine, tested in combination against five *Aspergillus* spp. isolates, resulted in synergistic cidal activity with fractional inhibitory concentration indices at least 2 dilutions lower in the MIC than for each drug. Synergy between terbinafine and azole antifungals against *Aspergillus* spp. is thought to be due to the combined effects of the drugs on different stages of the ergosterol biosynthesis pathway.[29]

The combination of voriconazole with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor (GM-CSF)–treated polymorphonuclear neutrophils (PMNs) increases inhibitory hyphal growth activity of *A. fumigatus*. In contrast, addition of voriconazole to GM-CSF–treated monocytes does not significantly increase inhibition of hyphal growth beyond that of either voriconazole or GM-CSF used alone with monocytes.[30]

Voriconazole was active (MIC 1 μg/mL) against an itraconazole-resistant clinical isolate (MIC >16 μg/mL) of *A. fumigatus*. *ERG11* was cloned by RT-PCR and then sequenced for an itraconaozle-susceptible and -resistant isolate of *A. fumigatus*. Molecular examination of both isolates revealed that the likely mechanism conferring resistance to itraconazole was a change from histidine to arginine at position 370 in the predicted protein encoded by *ERG11*.[31]

Scedosporium spp. and *Fusarium* spp.

Voriconazole MICs for *S. apiospermum* is 0.5 μg/mL (determined at 100% growth inhibition); MICs for itraconazole and amphotericin B are significantly higher: 2 and 8 μg/mL, respectively. Little or no in vitro activity was noted for these antifungal agents against *S. prolificans* (MIC at 100% inhibition of growth >8 μg/mL for each agent).[32]

Voriconazole has MICs against *Fusarium* spp. comparable to those against amphotericin B and lower than those with itraconazole.[8-10]

Table 1. Comparative In Vitro Antifungal Activity of Voriconazole and Other Antifungal Agents Versus *Aspergillus* spp., *Fusarium* spp., and *Candida* spp.

		Range of MIC_{90} (µg/ml)					
Organism	**Voriconazole**	**Fluconazole**	**Itraconazole**	**Ketoconazole**	**Amphotericin B**	**Flucytosine**	**Reference**
Aspergillus							
flavus	1 (n = 15)[a]		1		8		7
	0.5 (n = 10)		0.25		1		8
	0.36 (n = 27)		0.25		1.63		9[b]
	0.57 (n = 11)		0.1		1.07		10[b]
	0.5 (n = 7)		0.125		2		11
fumigatus	1 (n = 142)		1		4		7
	0.5 (n = 10)		0.5		0.5		8
	0.27 (n = 24)		0.47		2.18		9[b]
	0.29 (n = 12)		0.24		1		10[b]
	0.5 (n = 35)		0.5		2		11
	0.5 (n = 150)		0.25		1		12
	1 (n = 62)		1		2		13
	0.39 (n = 25)	100			1.56		14
	0.5 (n = 20)				1		15
nidulans	0.5 (n = 3)		0.5		2		9[b]
	0.125 (n = 2)		0.06		2		11
niger	4 (n = 36)		4		4		7
	0.32 (n = 17)		0.59		0.75		9[b]
	0.5 (n = 7)		0.5		2		12
	0.39 (n = 15)	100			1.56		15
terreus	0.37 (n = 9)		0.17		4.32		9[b]
	0.5 (n = 8)		0.125		1		11
Fusarium							
oxysporum	1 (n = 4)		22.6		4		9[b]
	4 (n = 6)		8		2		10
solani	4 (n = 10)		>16		2		8
	4.16 (n = 18)		>16		4.9		9[b]
	10.5 (n = 6)		8		1.31		10[b]
Candida							
albicans	0.12 (n = 181)	8	0.12				16
	0.015 (n = 90)	0.25	0.12				17
	0.06 (n = 660)	1.0	0.25				18
	0.06 (n = 206)	2	0.25		1	4	19
	0.5 (n = 100)	32					20
	0.0625 (n = 513)	0.5	0.125	0.125	1	1	21
	0.125 (n = 183)	64	4		0.5	0.5	22
	0.25 (n = 24)	≥64	0.5	>16			23
glabrata	2 (n = 124)	32	4				16
	1 (n = 21)	16	1				17
	2 (n = 217)	64	4				18
	1 (n = 77)	64	4		2	0.25	19
	2 (n = 66)	16	4	2	1	4	21
	0.25 (n = 12)	≥64	2		0.25	0.25	22
	0.25 (n = 12)	32	1	1			23
krusei	2 (n = 20)	≥64	4				16
	1 (n = 33)	64	2				18
	1 (n = 17)	128	2		2	64	19
	0.5 (n = 42)	64					20
	0.25 (n = 11)	≥64	1		0.5	16	22
	0.5 (n = 3)	>64	0.5	0.5			23
parapsilosis	0.06 (n = 36)	1	0.25				17
	0.12 (n = 221)	2	0.5				18
	0.25 (n = 40)	8	0.5		2	1	19
	0.12 (n = 40)	2					20
	0.125 (n = 78)	1	0.5	0.5	1	0.25	21
	0.25 (n = 3)	32	0.25	0.5			23

MIC_{90} = 90% of minimum inhibitory concentration.
[a]Number of isolates.
[b]Geometric mean MIC.

MIC determination at 100% growth inhibition may more clearly and reliably detect azole resistance. The MIC_{90} of voriconazole at this more stringent breakpoint in 5 isolates of *F. moniliforme*, 6 isolates of *F. oxysporum*, and 12 isolates of *F. solani* were 2, 8 and 8 μg/mL, respectively.[10] Voriconazole has low fungicidal activity versus *Fusarium* spp.[8,15,28]

Candida spp.

Voriconazole is fungistatic, yet highly active, against isolates of *Candida* spp., with *C. albicans* being the most susceptible (Table 1). Maximal fungistatic activity for *C. albicans* occurs at voriconazole concentrations ≥4 times the MIC; maximal fungistatic activity for *C. glabrata* and *C. tropicalis* occurs at concentrations equal to the MIC (MIC 0.007–4 μg/mL). Voriconazole concentrations producing 50% and 90% of the maximal effect (EC_{50} and EC_{90}) were either equivalent (EC_{50}) or showed little variability (EC_{90}) at 8-, 12-, and 24-hour time points, thus implying that increasing the concentration of voriconazole does not improve the rate of fungistatic activity.[33]

Voriconazole, like fluconazole, has the ability to complement PMNs, increasing fungicidal activity of these phagocytic cells for *Candida* spp.[34] Additionally, voriconazole may act against *Candida* spp. by interfering with critical host/fungi interactions in addition to having direct inhibitory activity.[35] These pharmacodynamic interactions have been reviewed previously.[36] Voriconazole has a positive, concentration-dependent, post-antifungal effect (PAFE) against *C. albicans* when assayed in the presence of 10% human serum; a negative PAFE is observed when no serum is present. Voriconazole-pretreated *C. albicans* isolates are more susceptible than untreated isolates to subsequent reexposure to the antifungal agent. The combination of pretreatment with voriconazole followed by exposure to both serum and PMNs results in the greatest inhibition of fungal growth.[37]

Combination therapy with voriconazole and terbinafine was synergistic in 23 of 39 isolates, and additive for 16 of 39 isolates. Of the 39 clinical isolates, 13 strains were resistant to fluconazole (MIC ≥64 μg/mL), with voriconazole cross-resistance (voriconazole MICs >1 μg/mL) in 8 strains. Nine of the fluconazole-resistant strains demonstrated synergistic effects when voriconazole was combined with terbinafine. For the 8 voriconazole cross-resistant strains, combination voriconazole–terbinifine resulted in synergistic activity in all isolates, reducing the median voriconazole MIC from 16 to 0.03 μg/mL.[38]

Against 51 strains of *C. albicans*, the combination of flucytosine and voriconazole was synergistic in 27, additive in 16, and indifferent in 8 of the strains. The combina-

Table 2. Comparative In Vitro Antifungal Activity of Voriconazole and Other Antifungal Agents Against Other Yeast, Molds, and Dermatophytes

	Range of MIC_{90} (μg/mL)				
Organism	**Voriconazole**	**Fluconazole**	**Itraconazole**	**Amphotericin B**	**Reference**
Absidia corymbifera	16 (n = 10)[a]		0.5	0.25	7
Blastomyces dermatitidis	0.1 (n = 5)		0.06	0.14	10[b]
	0.25 (n = 100)		0.125	0.5	24
Chrysosporium keratinophilum	0.20 (n = 10)	100		1.56	14
Cladophialophora bantiana	0.12 (n = 10)		0.12	0.5	7
Coccidiodes immitis	0.25 (n = 104)		0.5	0.5	24
Cryptococcus neoformans	0.25 (n = 38)	16	1	1	10[b]
	0.07 (n = 50)		0.14		25[b]
	0.12 (n = 566)	6.25		0.2	26
Exophiala dermatitidis	0.25 (n = 10)		0.5	1	7
Fonsecaea pedrosoi	0.06 (n = 10)		0.25	1	9
Geotrichum candidum	0.39 (n = 23)	25		1.56	14
Histoplasma capsulatum	0.06 (n = 5)	16	0.06	0.42	10[b]
Phialophora parasitica	0.25 (n = 10)		>16	2	7
	0.25 (n = 100)		0.06	1	24
Pseudallescheria boydii	0.33 (n = 6)		0.76	2.6	10[b]
Rhizopus arrhizus	16 (n = 10)		2	0.25	7
	18.37 (n = 5)		0.43	0.57	10[b]
Scopulariopsis brevicaulis	3.13 (n = 24)	100		6.25	14
Sporothrix schenckii	>16 (n = 10)		4	4	7
	16 (n = 5)		0.5	1.5	10[b]
Syncephalastrum racemosum	6.25 (n = 10)	100		0.78	14

MIC_{90} = 90% of minimum inhibitory concentration.
[a]Number of isolates.
[b]Geometric mean MIC.

tion of amphotericin B and voriconazole was synergistic in 25, additive in 15, and indifferent in 11 of the strains. Antagonism was not demonstrated for either combination.[39]

The impact of mechanisms of azole resistance (multidrug efflux transport, alteration of affinity to CYP51A1) has been evaluated for voriconazole. In a *Saccharomyces cerevisiae* model, expression of *C. albicans* multidrug efflux transporters *CDR1* and *CDR2* and major facilitators *MDR1* and *FLU1* conferred resistance to voriconazole. Alteration of affinity was demonstrated using mutant CYP51A1 proteins and was observed to parallel changes of affinity to fluconazole.[40]

OTHER YEASTS, MOLDS, AND DERMATOPHYTES

Voriconazole has demonstrated in vitro activity for a variety of other fungi (Table 2). Voriconazole is more potent than itraconazole versus isolates of *Cryptococcus neoformans* and *C. neoformans* var. *neoformans*. Nearly all fluconazole-susceptible isolates of these 2 species of *Cryptococcus* are inhibited by voriconazole and itraconazole concentrations ≤0.5 µg/mL, yet the percentage of isolates having MICs ≤0.125 µg/mL is greater for voriconazole than itraconazole. Increases in fluconazole MICs for *C. neoformans* and *C. neoformans* var. *neoformans* correspond to increases in MICs for itraconazole and voriconazole.[25,26]

Voriconazole is more active than amphotericin B, itraconazole, or fluconazole against the yeast *Trichosporum* spp.[14,41] and more active than fluconazole or amphothericin B against *Geotrichum candidum*.[14] Voriconazole has limited activity against *Rhodotorula* spp.[14,24] and *Malassezia* spp.[42]

Voriconazole is active against the mold forms of the dimorphic fungi *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*. Although only fungistatic for *C. immitis*, both voriconazole and itraconazole were fungicidal for many *B. dermatitidis* isolates and some *H. capsulatum* isolates.[24] Against other molds, voriconazole has consistently shown poor activity with *Rhizopus* spp. and is not active against isolates of *Apophysomyces elegans* or *Rhizomucor pusillus*.[14,24,43] Both amphotericin B and itraconazole were more active than voriconazole for *Sporothrix schenckii*.[44-46]

Against the dermatophytes *Microsporum* spp. and *Epidermophyton floccosum*, voriconazole was at least as active as fluconazole or griseofulvin,[14,47] but less active than itraconazole or terbinafine.[47]

Pharmacokinetics

Voriconazole exhibits good oral bioavailability and wide tissue distribution, with hepatic metabolism and renal excretion of metabolites. Pharmacokinetic parameters for voriconazole in humans are summarized in Table 3.[48-51]

ABSORPTION

In humans, relative bioavailability reaches 90% and peak concentrations are attained in <2 hours.[51] Maximal serum concentrations of voriconazole following oral dosages of 200 mg twice daily are in the range of 2.12–4.8 µg/mL. Corresponding trough concentrations are 1.4–1.78 µg/mL.[48,49]

In animal models, the use of grapefruit juice in lieu of water resulted in both earlier detection and greater serum concentrations after oral administration of voriconazole. Time to reach steady-state serum concentrations was not established.[52] There are currently no data regarding the effect of grapefruit juice on voriconazole absorption in humans.

DISTRIBUTION

Distribution of voriconazole is rapid and extensive throughout tissues, with a volume of distribution of approximately 2 L/kg.[51] Fifty-eight percent of serum concentrations are bound to plasma proteins.[51] Wide distribution of voriconazole is supported by animal models in which fungal burden is decreased in the myocardium,[53] brain and lung,[54-56] and kidney and liver tissues.[54,56] Human case reports have described cerebrospinal fluid (CSF) concentrations between 29% and 68% of concurrent serum concentrations.[48,50,57]

METABOLISM AND ELIMINATION

Voriconazole undergoes extensive hepatic metabolism. Three major and 5 minor metabolites have been identified with the CYP2C9, CYP2C19, and CYP3A4 hepatic isoenzyme systems involved.[58] The affinity of voriconazole is greatest for CYP2C19, an enzyme with genetic polymorphism. On average, a fourfold higher voriconazole concentration (AUC) was reported in a study involving healthy white and Japanese volunteers (populations expected to be poor metabolizers) than in homozygous extensive metabo-

Table 3. Pharmacokinetic Parameters of Voriconazole in Humans

Parameter	Results	Comments	Reference
C_{max} (µg/mL)	3.31–3.39	1 h after iv or po administration	48
	2.12–4.8	at day 7 of therapy	49
	1.4–5.8	dose 12 mg/kg/d	50
C_{min} (µg/mL)	1.4–1.78	at day 7 of therapy	49
	1.4–4.8	dose 12 mg/kg/d	50
CSF concentration (µg/mL)	1.36–2.65		48
	0.8–3.1		49
t_{max} (h)	<2		51
$t_{1/2}$ (h)	6		51
Plasma protein binding (%)	58		51
V_d (L/kg)	2		51

C_{max} = maximum concentration; C_{min} = minimum concentration; CSF = cerebrospinal fluid; $t_{1/2}$ = half-life; t_{max} = time to C_{max}; V_d = volume of distribution.

lizers. Heterozygous extensive metabolizers had, on average, a twofold higher voriconazole exposure than homozygous extensive metabolizers.

Voriconazole has the least affinity for CYP3A4, with in vitro studies demonstrating significantly less inhibition of metabolic activity resulting from voriconazole than ketoconazole and itraconazole. Voriconazole *N*-oxide, a major metabolite of voriconazole, inhibits CYP2C9 and CYP3A4 to a greater extent than CYP2C19.[27] Kinetics in humans are nonlinear; this may be due to saturable, first-pass metabolism and reduced systemic clearance. The mean half-life of voriconazole is about 6 hours.[51] Less than 5% of the dose administered is eliminated renally as unchanged drug.[58]

Drug Interactions

Drugs cleared through the CYP450 system may interact through complex effects on this microsomal enzyme system by either the target drug or voriconazole. Voriconazole serum concentrations are significantly reduced by rifampin and rifabutin and are likely to be significantly reduced by carbamazepine and long-acting barbiturates. Therefore, voriconazole coadministration with these agents is contraindicated.[27] Reduced voriconazole concentrations through concomitant administration of phenytoin may be offset by doubling the dose of voriconazole.[59] Medications that have demonstrated only minor or no significant effects on voriconazole pharmacokinetics include cimetidine, ranitidine, erythromycin, azithromycin, and indinavir.[27,60]

The metabolism of other drugs that are substrates of the CYP450 metabolic system may be inhibited by voriconazole. Drugs contraindicated for coadministration with voriconazole include sirolimus (sirolimus concentrations significantly elevated); terfenadine; astemizole; cisapride, pimozide, and quinidine (due to potential QT prolongation and possible occurrence of torsade de pointes); and ergot alkaloids (possible ergotism). Dosage reductions for cyclosporine (one-half the original dose) and tacrolimus (one-third the original dose) are recommended upon initiation of voriconazole in patients stabilized on these medications. Frequent monitoring of cyclosporine or tacrolimus blood concentrations is recommended.[27,61] In vitro studies indicate that voriconazole inhibits hepatic metabolism of lovastatin, midazolam, and felodipine, and it is likely that this inhibition extends to the entire class of each of these representative drugs. Other drugs or drug classes that may require monitoring for potentiation of effects and/or toxicity include omeprazole, phenytoin, warfarin, sulfonylureas, and vinca alkaloids.[27,59,62] Voriconazole has only minor or no significant effects on concentrations of prednisolone, digoxin, and mycophenolic acid.[27,63,64]

Interactions between voriconazole and medications used to treat patients with HIV are complex. Voriconazole may inhibit metabolism of protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). In return, PIs (e.g., saquinavir, amprenavir, nelfinavir) may inhibit the metabolism of voriconazole; NNRTIs may either inhibit the metabolism of voriconazole (e.g., delavirdine, efavirenz) or induce the metabolism of voriconazole (e.g., efavirenz, nevirapine).[27]

Clinical Trials

ASPERGILLOSIS

In a recent study, voriconazole was compared with amphotericin B for primary therapy of invasive aspergillosis (IA) in immunocompromised patients.[65] Antifungal regimens were as follows: intravenous voriconazole 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours for at least 7 days, followed by oral voriconazole 200 mg twice daily up to a total of 12 weeks; or intravenous amphotericin B 1.0–1.5 mg/kg/d for 14 days. Patients could be switched to other licensed antifungal therapy (OLAT) if they failed to respond or were intolerant of initial randomized therapy. At week 12 of therapy, voriconazole was not inferior and was statistically superior to amphotericin B (primary endpoint): 52.8% of patients receiving voriconazole and 31.6% of those receiving amphotericin B had a successful outcome (absolute difference 21.2%; 95% CI 10.4% to 32.9%). This approximate 20% absolute difference in favorable outcome for voriconazole was consistent upon retrospective examination of stratified populations. Categories into which patients were stratified included pulmonary infection only, extrapulmonary infection, allogeneic hematopoietic-cell transplantation, neutropenic hematologic condition, other immunocompromising condition, neutropenia, no neutropenia, definite aspergillosis, and probable aspergillosis.

Due to sizable differences in treatment duration at the end of randomized therapy (median 77 d for voriconazole vs. 11 d for amphotericin B), safety was compared between the voriconazole and amphotericin B plus OLAT regimens. Visual disturbances occurred more frequently in voriconazole-treated patients compared with amphotericin B plus OLAT-treated patients (33.2% vs. 4.3%); most patients did not have clinically meaningful changes in bedside visual acuity, visual field testing, or fundoscopy results throughout the study period. Hallucinations also occurred in a higher percentage of voriconazole-treated patients (6.6% vs. 1.6% for amphotericin B plus OLAT-treated patients). Rates of abnormalities in hepatic function tests were similar between the groups; abnormalities in renal function tests occurred more often in patients receiving amphotericin B plus OLAT.[65]

A second open-label trial assessing the efficacy, safety, and toleration of voriconazole in the treatment of acute IA in immunocompromised patients was reported by Denning et al.[66] The primary efficacy endpoint of this uncontrolled, multicenter study was clinical response as assessed by the investigator at the end of treatment. Sixty patients deemed to have definite or probable acute IA received voriconazole as primary therapy, with 31 patients naïve to antifungals and 29 having received low doses of alternate antifungals for <7 days. Fifty-six patients received voriconazole

as salvage therapy. The most common site of infection was the lungs (70%), followed by cerebral disease (16%) and disseminated disease (5%).

At the end of therapy, the infections of 16 of 116 (14%) evaluable patients had a complete response to voriconazole, 40 (34%) had a partial response, and 24 (21%) had a stable response. The infections of 36 (31%) patients failed to respond to voriconazole therapy. Two patients with complete response subsequently died, 1 of underlying disease and 1 with relapse of IA. Sixteen patients with partial response died. Death occurred in 32 of the patients classified as treatment failures at the end of therapy. Factors that positively influenced outcome included underlying disease of a hematologic disorder and pulmonary and tracheobronchial aspergillosis versus other sites of infection. A definite diagnosis of IA negatively influenced outcome compared with probable disease. Additionally, patients receiving voriconazole as salvage therapy did not respond as well as those receiving voriconazole as primary therapy. Ninety-five of 623 adverse events were attributed to voriconazole, the most common being rash, visual disturbance, and elevated liver function. Five of 203 serious adverse events were thought to be due to voriconazole (1 each of hypoglycemia and pneumonitis, abnormal liver function, worsening of psoriasis; 2 of rash).[66]

Patients from the study by Denning et al.[66] were compared with historical controls receiving standard antifungal therapy for definite or probable acute IA.[67] Case-matched populations had received ≤5 days of therapy. Based on clinical interpretation, the response at the end of therapy and survival rate at 90 days in patients receiving voriconazole compared favorably with that of the historical controls. No formal statistical hypothesis testing was performed.

Case reports describe the use of voriconazole in the treatment of a fungal brain abscess,[48] meningitis,[50] and infection of bone within the skull.[68] Only the patient with the fungal brain abscess had an underlying immunocompromised state. Failed antifungal regimens included amphotericin B, liposomal amphotericin B, and itraconazole (despite dosage based on serum concentrations). Length of voriconazole therapy was approximately 6, 2, and 14 months, respectively. Although the patient with the fungal brain abscess died of refractory leukemia, there was no evidence of recurrence of the aspergillus infection. The patient treated for meningitis remained well 12 months after completion of voriconazole therapy. No further signs of disease progression were noted over the 5-year follow-up for the patient with the skull bone infection.

Voriconazole displays equal or superior efficacy compared with amphotericin B or standard therapy in the treatment of acute IA in immunocompromised patients. Use of voriconazole for aspergillosis is further supported by the fact that serum voriconazole concentrations exceed the in vitro MIC values versus most *Aspergillus* spp. and that it has fungicidal activity against *A. fumigatus* and *A. flavus*. Patients with underlying hematologic disorders are good candidates for voriconazole therapy. Use of voriconazole in patients with solid organ transplantation or AIDS is more likely to be complicated by drug interactions. There is little information regarding the use of voriconazole for the treatment of central nervous system (CNS) aspergillosis. However, due to limited therapeutic options for these patients and the fact that voriconazole does enter the CSF, it may be an alternative. Voriconazole has advantages over other antifungal agents indicated for the treatment of IA: more reliable pharmacokinetics than itraconazole and oral formulations not available with liposomal amphotericin B or caspofungin. As with itraconazole, however, the cyclodextran excipient in the intravenous preparation of voriconazole precludes its use in patients with significant renal dysfunction (see *Safety* and *Dosing* sections for greater discussion).

INFECTIONS CAUSED BY SCEDOSPORIUM, FUSARIUM, AND OTHER RARE FUNGAL PATHOGENS

Subjects reported by Torre-Cisneros et al.[69] had a variety of culture-proven scedosporium infections. Outcome was assessed at 90 days (in ongoing patients) or at the end of therapy. Sixty-three percent (17 of 27) of patients with *S. apiospermum* infections and 29% (2 of 7) of those with *S. prolificans* infections had a satisfactory outcome. Response to voriconazole did not depend on the location or number of sites of scedosporium infection.

Five case reports describe treatment of *S. apiospermum* with voriconazole.[57,70-73] Sites of infection included the skin, lungs, and CNS. Patients had the following underlying immunosuppressive conditions: acute myeloid leukemia, chronic granulomatous disease, chronic high-dose steroid use, and organ transplantation. Antifungal agents used included amphotericin B (alone or in combination with flucytosine), lipid preparations of amphotericin B, itraconazole, and intravenous miconazole. Failure of fungal infection to respond to these treatments prompted switching to voriconazole. In each case, clinical improvement was noted after initiation of voriconazole, and resolution of infection was documented at follow-up (7–12 m).

A case of severe ulcerative hypopyon keratitis caused by *Fusarium solani* was successfully treated with voriconazole.[74] In attempts to optimize ocular concentrations, voriconazole10 µg/0.1mL was injected once intracamerally, irrigated within the anterior chamber of the eye (3-µg/mL solution), and applied topically to the eye (at a concentration of 1%) every half-hour. Voriconazole was continued for 8 weeks, healing occurred, and the corneal graft remained clear. Transient elevation of liver enzymes was the only reported adverse event from either the topical or systemic administration of voriconazole in this patient.

In a case of pacemaker-related endocarditis from disseminated acremonium infection, voriconazole and surgical removal of the pacemaker and electrode resulted in clinical cure.[75] Voriconazole failed to eradicate *Paecilomyces lilacinus*, the causative agent in a localized skin infection.[76] Analyses of voriconazole use for patients with other rare or resistant fungal pathogens was reported by Perfect et al.[77]

Although occurrence of infections due to rare fungal pathogens is on the rise, clinical data, as you would expect, are limited. Microbiologic activity and clinical efficacy of amphotericin B and other azoles for treatment of *Scedosporuim* and *Fusarium* spp. have been poor. Voriconazole has in vitro activity against *S. apiospermum* and *Fusarium* spp. comparable or superior to that of amphotericin B and itraconazole. This, together with data described in case reports, lend support for use of voriconazole in treatment of these rare or resistant fungal pathogens.

CANDIDIASIS

A single randomized clinical trial on treatment of esophagoscopy- and mycology-proven esophageal candidiasis has been published.[78] Four hundred eighty-seven patients received either voriconazole 200 mg twice daily or fluconazole 400 mg on day 1 followed by 200 mg/d for 2–6 weeks in a double-blind, double-dummy fashion. Patients were immunocompromised: 94% (n = 368) had AIDS and 6% (n = 23) had other underlying diseases; based on clinical symptoms, patients had a diagnosis of esophagitis with or without concomitant oropharyngeal candidiasis. Primary analysis of efficacy was based on response to treatment as assessed by esophagoscopy; secondary analysis of efficacy was determined by symptomatic assessment. Primary and secondary endpoints were evaluated on day 43 or at the end of therapy, with success defined as cured (normal endoscopy or resolution of all symptoms) plus improved (abnormal endoscopy but improvement of ≥1 grades or improvement of ≥1 symptoms and no worsening of any symptom) compared with baseline.

At the end of therapy, the success rate as assessed by esophagoscopy was 98.3% for voriconazole-treated patients and 95% for fluconazole-treated patients; success rate evaluated by symptoms was 88.0% and 91.1%, respectively, of patients in the voriconazole and fluconazole groups. Microscopy and mycologic culture from a brush biopsy or tissue biopsy of esophageal lesions identified *C. albicans* in 179 (89.5%) of voriconazole-treated patients and 175 (91.6%) of fluconazole-treated patients. Other *Candida* spp. were isolated, most in association with *C. albicans*. Voriconazole MICs for the candida isolates were 25- to 250-fold lower than those for fluconazole, yet rose correspondingly as fluconazole MICs rose. MICs were not correlated with clinical outcome for the voriconazole-treated patients: MICs for patients successfully treated with voriconazole ranged from 0.006 to 1.0 μg/mL; MICs for patients who failed voriconazole therapy ranged from 0.012 to 0.098 μg/mL. No endoscopic failures were demonstrated in patients from which non-albicans *Candida* spp. were isolated; it was presumed that these isolates were not pathogenic, rather simply coinhabitants with pathogenic *C. albicans*.[78]

Although voriconazole is effective in the treatment of esophageal candidiasis and oropharyngeal candidiasis, a distinct advantage over the use of fluconazole has not been established. Continued increase in patient populations at risk for serious mycoses, along with persistently rising rates of non-albicans *Candida* spp. that cause disease, may afford a place for voriconazole in the future. Continued surveillance and research will more clearly define voriconazole's role in the treatment of candidal disease.

FEBRILE NEUTROPENIA

In a randomized, international, multicenter trial, voriconazole was compared with liposomal amphotericin B as empiric antifungal therapy in persistently febrile neutropenic patients.[79] The study was designed to demonstrate noninferiority of voriconazole by a difference in success rate no greater than –10% for a composite endpoint of breakthrough fungal infection, survival for 7 days beyond the end of therapy, no discontinuance of therapy prematurely, resolution of fever during the period of neutropenia, and successful treatment of any baseline fungal infection. Analysis was performed on a modified intent-to-treat basis for 415 patients receiving voriconazole and 422 patients receiving liposomal amphotericin B. The overall success rate for the composite endpoint was 26% in voriconazole-treated patients and 30.6% in liposomal amphotericin B–treated patients. The lower bound of the 95% CI for the difference in treatment groups fell just outside the predefined limit (–10.6% to 1.6%). Exploratory assessment of individual composite endpoints exhibited fewer proven and probable breakthrough fungal infections with voriconazole, with 8 (1.9%) versus 21 (5.0%) ($p = 0.02$). Patients receiving voriconazole in the stratified cohort of high risk for fungal infection (those with allogeneic transplants or relapsed leukemia) demonstrated an even more pronounced reduction in invasive fungal infections compared with liposomal amphotericin B (2 of 143, 1.4% vs. 13 of 141, 9.2%; $p = 0.003$). No significant differences were found in the other individual composite endpoints.

Patients receiving voriconazole reported fewer cases of severe infusion-related reactions, but experienced more episodes of transient visual changes and hallucinations. Elevations in serum aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels occurred at similar rates between the treatment groups. Elevations in serum bilirubin levels of ≥1.5 times above baseline occurred more often in patients receiving liposomal amphotericin B (17.6% for voriconazole vs. 23.0% for liposomal amphotericin B; $p = 0.05$). Nephrotoxicity, as defined as serum creatinine >1.5 times baseline, was less frequent in the voriconazole treatment arm (11% for voriconazole vs. 19% for liposomal amphotericin B; $p < 0.001$); occurrence of nephrotoxicity was the same for patients with serum creatinine >3 times baseline (5%).[79]

Voriconazole's usefulness as empiric treatment for patients with febrile neutropenia remains unresolved.[80,81] In the only published study of voriconazole in persistently febrile neutropenic patients, the 95% CI in the primary analysis fell statistically just outside the lower limit for noninferiority.[81] Although reasons for this may be due to factors other than the antifungal agent's value in the treat-

ment of fungal disease (i.e., death due to progressive underlying neoplastic disease, biases introduced due to the open-label nature of the trial[80]), voriconazole noninferiority to liposomal amphotericin B cannot be concluded. To further complicate the interpretation, secondary analyses of individual composite endpoints within this trial were exploratory assessments not intended to be a primary determination of superiority of outcome.

PEDIATRIC PATIENTS

One study described voriconazole therapy in 69 children between the ages of 9 months and 15 years (median 7 y) for treatment of an invasive fungal infection.[82] All children were refractory to or intolerant of conventional antifungal therapy. Fifty-eight children had proven or probable fungal infection. The most common underlying conditions were hematologic malignancies (27 pts.) and chronic granulomatous disorder (13), and the most frequent fungal pathogens were *Aspergillus* spp. (72%) and *Scedosporium* spp. (14%). Intravenous voriconazole 6 mg/kg was administered every 12 hours for 2 doses, followed by 4 mg/kg every 12 hours. Patients could be switched to oral therapy.

Twenty-six patients (45%) had a complete or partial response at the end of voriconazole therapy; 4 patients had a stable response and 25 failed therapy. Twenty-three adverse events were considered treatment-related, with 3 patients withdrawn from voriconazole therapy due to toxicity. Toxicities included photosensitivity reaction plus cheilitis (1 child) and elevated hepatic transaminases (2 children). Common adverse effects included elevation in transaminases or bilirubin, rash, abnormal vision, and photosensitivity reaction (13.8%, 13.8%, 5.2%, and 5.2% of patients, respectively.) Median plasma concentration of voriconazole was 1566 ng/mL for children receiving ≥4 mg/kg intravenously twice daily, which was lower than median plasma concentrations from a control population of adults (5671 ng/mL; 4 mg/kg twice daily).[82]

These data lend support for the use of voriconazole as an alternative in the pediatric population for treatment of invasive fungal infections unresponsive to conventional antifungal agents. Adverse events reported are similar to those described in adults. Lower median plasma concentrations of voriconazole compared with those in adults may imply more rapid excretion in the pediatric population. Additional clinical trials, including kinetic exploration, are needed to further clarify voriconazole's role in treatment of fungal infections in children.

Safety and Tolerability

The most commonly reported adverse events with voriconazole include visual disturbances and elevations in liver function tests.[65,66,79] Visual disturbances, occurring in 8–44% of patients, have been described as enhanced perception to light and mild to moderate in severity, thus not requiring drug discontinuance.[66,79] No residual visual adverse effects occurred in these patients. Although the mechanism of visual disturbance is not known, an investigation of the ocular effects of voriconazole showed a reduction in the amplitude of electroretinogram waveforms a and b within the retina, thus impairing the photoreceptor retinal systems of both the cones and rods during conditions of bright as well as dim illumination.[67] Visual disturbances may be associated with higher plasma concentrations and/or doses. Monitoring of visual acuity, visual field, and color perception is advised if therapy extends beyond 28 days.[27]

Liver function should be determined prior to and periodically throughout voriconazole therapy. Abnormalities in liver function tests may be associated with higher voriconazole dosages and/or serum concentrations, but generally resolve either with continued therapy or dosage modification, including drug discontinuance. Uncommon cases of serious hepatic reactions were reported during clinical trials and consisted of clinical hepatitis, cholestasis, and fulminant hepatic failure including fatalities.[27]

Adverse dermatologic reactions have been reported. In clinical trials, treatment was discontinued in patients who developed a skin rash.[66] In 1 case report, a patient exhibited facial photosensitivity to sunlight and developed biopsy-confirmed discoid lupus vulgaris skin lesions in the sun-exposed areas. Use of sunblock alleviated the development of skin lesions, enabling the patient to continue therapy. Resolution of facial redness was attained within 3 months of discontinuing voriconazole.[68]

Voriconazole has limited aqueous solubility; therefore, the intravenous preparation is combined with the solubilizing agent sulfobutyl ether β-cyclodextrin sodium (SBECD). SBECD is pharmacologically inert, does not affect the pharmacokinetics of voriconazole, and is renally cleared at a rate consistent with glomerular filtration. It does not accumulate with repeated dosing in subjects with normal renal function, as evidenced by a half-life of 1.6 hours on both days 1 and 10. Accumulation of SBECD does occur in subjects with moderate to severe renal impairment (serum creatinine >2.5 mg/dL); therefore, it is recommended that the oral preparation be used for patients with creatinine clearance <50 mL/min. In animal toxicology studies, the minimal single lethal dose was >2000 mg/kg. Obstruction of renal tubules and single-cell necrosis in the liver of rats with doses ≥3 g/kg indicate borderline toxicity in these organs.[67]

Voriconazole has been shown to cause teratogenicity in animals and carries a pregnancy category D rating.[27]

Formulation/Dosage and Administration

Both intravenous and oral formulations of voriconazole are available.[27] The intravenous formulation comes in a 30-mL vial as a single-dose, unpreserved product containing 200 mg of voriconazole SBECD. The powder is reconstituted with 19 mL of water for injection (20 mL extractable volume) providing a solution containing 10 mg/mL of voriconazole and 160 mg/mL of SBECD. The reconstituted solution should be diluted to ≤5 mg/mL prior to ad-

ministration and infused over 1–2 hours at a maximum rate of 3 mg/kg/h. Oral tablets contain 50 or 200 mg of voriconazole. Average wholesale prices are: $7.81 per 50-mg tablet, $31.25 per 200-mg tablet, and $106.25 per 200-mg vial.[83]

The recommended dosage of voriconazole for the treatment of adults with invasive aspergillosis and infections due to *Fusarium* spp. and *S. apiospermum* is 6 mg/kg intravenously every 12 hours for 2 doses, followed by a maintenance dose of 4 mg/kg every 12 hours. Voriconazole tablets may be used once the patient can tolerate medications given by mouth. Oral maintenance doses are 200 mg every 12 hours for patients weighing >40 kg and 100 mg every 12 hours for patients weighing <40 kg. Oral dosages may be increased in light of inadequate patient response (to 300 mg or 150 mg every 12 hours, respectively).

The manufacturer recommends standard loading-dose regimens, with reduction of the maintenance dose by 50% in patients with mild to moderate hepatic cirrhosis and use of oral voriconazole in patients with renal dysfunction.

Economic Issues

Pharmacoeconomic evaluation based on reduction in hospital length of stay was assessed in a single study.[79] Generally, administration of voriconazole compared with liposomal amphotericin B afforded a median reduction in length of stay of 1 day, with the greatest reduction seen for patients having received allogeneic transplants or with relapsed leukemia (median 2 d).

A second measure by which decreased costs may be realized is through administration of agents with a greater margin of safety. Voriconazole has demonstrated decreased rates of adverse effects compared with amphotericin B or liposomal amphotericin B. Thus, it is reasonable to presume that this will favorably impact total healthcare expenditures. However, conclusions regarding cost savings are not forthcoming until more information is available.

Formulary Recommendation/Summary

Voriconazole's role in the empiric treatment of neutropenic patients with persistent fever or disseminated candidiasis has not been established. A favorable adverse effects profile and the availability of an oral preparation could potentially result in institutional cost savings by averting harmful drug effects and enabling earlier hospital discharge.

Demonstrated clinical efficacy in the treatment of acute IA in immunocompromised patients and efficacy in the treatment of some rare fungal pathogens will most likely impart formulary placement of voriconazole. Formulary addition is most likely at institutions with cancer centers, solid organ or bone marrow transplant centers, or those with significant cases of endemic mycoses.

Margaret M Pearson PharmD, Fellow, Department of Pharmacy Practice, School of Pharmacy, University of Mississippi, Jackson, MS

P David Rogers PharmD PhD, Assistant Professor of Pharmacy, Pharmaceutical Sciences, and Pediatrics, Colleges of Pharmacy and Medicine, University of Tennessee, Memphis, TN

John D Cleary PharmD, Associate Professor, Departments of Medicine and Pharmacy Practice, Schools of Medicine and Pharmacy, University of Mississippi

Stanley W Chapman MD, Professor of Medicine and Associate Professor of Microbiology, School of Medicine, Departments of Medicine and Microbiology, University of Mississippi Medical Center, Jackson, MS

Reprints: Margaret M Pearson PharmD, Department of Pharmacy Practice, School of Pharmacy, University of Mississippi, 2500 N. State St., Jackson, MS 39216-4505, FAX 601/984-2618, E-mail mpearson@pharmacy.umsmed.edu

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EXTRACTO

OBJETIVO: Repasar la farmacología, susceptibilidad in vitro, farmacocinética, eficacia clínica y los efectos adversos de voriconazol, un agente antifúngico triazólico.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda en el banco de datos de MEDLINE en idioma inglés para el período de 1990 a Junio 2002. Se incluyeron fuentes suplementarias de extractos de programas presentadas por las organizaciones llamadas "Interscience Conference on Antimicrobial Agents and Chemotherapy" y "Infectious Disease Society of America" para el periodo de 1996 a 2001, e información del manufacturero disponible vía la página web de la Administración de Alimentos y Medicamentos.

SELECCIÓN DE ESTUDIOS: Se seleccionó todos los estudios publicados y no publicados e extractos que citaron a voriconazole.

SÍNTESIS DE DATOS: Se ha demostrado que voriconazole tiene actividad in vitro contra muchos hongos y una variedad de mohos y dermatofitos. Se puede administrar el voriconazole por la vía oral o por inyección. El voriconazole tiene buena biodisponibilidad, distribución amplia en los tejidos incluyendo distribución en el sistema nervioso central, y metabolismo hepático. Interacciones con otras drogas pueden ocurrir por medio de inhibición de las isoenzimas CYP2C9, CYP2C19, y CYP3A4, resultando en alteraciones en los parámetros cinéticos de voriconazole o del agente interactivo. Se ha demostrado su eficacia en estudios abiertos y no comparativos de pacientes inmunocomprometidos y con aspergilosis. Reportes de casos describen su éxito en el tratamiento de patógenos fúngicos raros. Los efectos adversos mas comúnmente reportados incluyen disturbios visuales y elevaciones en las pruebas de funciones hepáticas.

CONCLUSIONES: Voriconazole tiene por lo menos una eficacia igual a la anfotericina B en el tratamiento de la aspergilosis invasiva aguda en pacientes inmunocomprometidos. Este también tiene eficacia similar a fluconazole en el tratamiento de candidiasis esofágica. El uso de voriconazole para la terapia empírica en pacientes con neutropenia y fiebre persistente permanece sin resolverse. Voriconazole en este instante cayo estadística afuera del limite bajo de no-inferioridad en comparación a la formulación anfotericina B en liposomas. Esto disminuyó el entusiasmo para este tipo de indicación hasta que se completen estudios adicionales. Dado los reportes de casos y de su eficacia in vitro, podría que voriconazole sea un agente útil en el tratamiento de otras enfermedades fungales.

Carlos da Camara

RÉSUMÉ

OBJECTIF: Revoir la pharmacologie, la sensibilité in vitro, la pharmacocinétique, l'efficacité clinique, et l'innocuité du voriconazole, un nouvel antifongique.

REVUE DE LITTÉRATURE: Une recherche informatisée MEDLINE limitée à la littérature anglaise couvrant la période de janvier 1990 à juin 2002 fut effectuée. Les abrégés des congrès Interscience Conference on Antimicrobial and Chemotherapy et de la Infectious Diseases Society of America couvrant la période de 1996 à 2001 ainsi que l'information de manufacturier accessible via le site Web de la FDA furent consultés.

SÉLECTION DE L'INFORMATION: Toutes les études et tous les abrégés publiés ou non citant le voriconazole furent sélectionnés.

RÉSUMÉ: Le voriconazole a démontré une activité in vitro contre plusieurs champignons, moisissures, et dermatophytes. Il peut être administré par voie parentérale et orale. Il démontre une bonne biodisponibilité, une grande distribution incluant le système nerveux central et un métabolisme hépatique. Des interactions médicamenteuses peuvent survenir via une inhibition du cytochrome CYP2C9, 2C19, et 3A4 résultant en une altération des paramètres cinétiques du voriconazole ou de l'autre agent. Son efficacité a été démontrée dans des études ouvertes non comparatives auprès de patients immunosupprimés atteints d'aspergillose. Des rapports de cas décrivent avec succès son utilisation dans le traitement d'infections fongiques rares. Les effets secondaires les plus souvent rapportés incluent des effets visuels et des élévations d'enzymes hépatiques.

CONCLUSIONS: Le voriconazole est au moins aussi efficace que l'amphotéricine B dans le traitement de l'aspergillose invasive aiguë chez les patients immunosupprimés. Il a une efficacité similaire au fluconazole dans le traitement de la candidose esopharyngée. Il n'a pas démontré une équivalence à l'amphotéricine B liposomale pour le traitement empirique des patients neutropéniques ayant une fièvre persistante. Ceci a diminué grandement l'enthousiasme pour son utilisation dans cette indication, le temps que des études additionnelles soient complétées. Selon les rapports de cas et la sensibilité in vitro, le voriconazole pourra devenir un agent utile dans le traitement d'infections fongiques moins fréquentes.

Marc M Perreault