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Voriconazole: A New Triazole Antifungal Agent

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Voriconazole is a second-generation azole antifungal agent that shows excellent in vitro activity against a wide variety of yeasts and molds. It can be given by either the intravenous or the oral route; the oral formulation has excellent bioavailability. The side effect profile of voriconazole is unique in that non–sight-threatening, transient visual disturbances occur in ~30% of patients given the drug. Rash (which can manifest as photosensitivity) and hepatitis also occur. The potential for drug-drug interactions is high and requires that careful attention be given to dosage regimens and monitoring of serum levels and effects of interacting drugs. Voriconazole has been approved for the treatment of invasive aspergillosis and refractory infections with *Pseudallescheria/Scedosporium* and *Fusarium* species, and it will likely become the drug of choice for treatment of serious infections with those filamentous fungi.

The 1990s witnessed an expansion of the antifungal armamentarium to include 2 new azole agents, fluconazole and itraconazole. These agents changed our approach to treating many fungal infections. However, neither was an ideal agent. Itraconazole was plagued by absorption problems; fluconazole had a limited spectrum of antifungal activity, and resistance was soon noted in immunosuppressed hosts who received long-term treatment. Second-generation triazole agents have been in development for the past decade. The first of these new agents to receive approval from the US Food and Drug Administration (FDA) is voriconazole, a synthetic derivative of fluconazole. Replacement of one of the triazole rings with a fluorinated pyrimidine and the addition of an α-methyl group resulted in expanded activity, compared with that of fluconazole. The development of voriconazole proceeded primarily because of this broadened antifungal spectrum.

IN VITRO ACTIVITY

The mechanism of action of voriconazole, similar to that of all azole agents, is inhibition of cytochrome P450 (CYP 450)–dependent 14α-lanosterol demethylation, which is a vital step in cell membrane ergosterol synthesis by fungi [1]. For yeasts, voriconazole appears to be fungistatic, as are other azoles. However, for some filamentous organisms, voriconazole and other second-generation azoles are fungicidal [2]. This effect may relate to the stronger avidity of the new azoles for the lanosterol 14α-demethylase found in molds, compared with that found in yeasts, which may allow more-complete interruption of ergosterol synthesis and lead to cell death.

Voriconazole is active against all *Candida* species, including *Candida krusei,* strains of *Candida glabrata* that are inherently fluconazole-resistant, and strains of *Candida albicans* that have acquired resistance to fluconazole (table 1) [2–6]. In general, the MICs of voriconazole for *C. albicans* are 1–2 log lower than the MICs of fluconazole. For some, but not all, fluconazole-resistant strains of *C. albicans,* MICs of voriconazole are higher than those noted for fluconazole-susceptible strains [6]. The MICs for *C. glabrata* and *C. krusei* are higher than those for other species, but they are still in the presumed susceptible range. Voriconazole shows good in vitro activity against other yeasts, including *Cryptococcus neoformans, Trichosporon beigelii,* and *Saccharomyces cerevisiae* [7–9].

Voriconazole appears to be broadly active against many species of *Aspergillus,* including *Aspergillus terreus,* which is often resistant to amphotericin B (table 2) [2, 10–14]. Time-kill curves demonstrate that dose-dependent killing of *Aspergillus* species is not as efficient as that noted for amphotericin B but is much more efficient than that noted for itraconazole [2]. Voriconazole appears to have reasonable activity against *Blas-*

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Table 1. In vitro susceptibilities of voriconazole compared with those of other antifungal agents that are active against common yeast-like species.

Species, antimicrobial agent	MIC_{50} range or value, μg/mL	MIC_{90} range or value, μg/mL	MIC range, μg/mL
Candida albicans			
Fluconazole	0.25–0.5	0.25–8	0.06 to >128
Itraconazole	0.03–0.125	0.12–0.25	0.01 to >8
Voriconazole	0.002–0.06	0.015–0.5	≤0.002 to >16
Candida tropicalis			
Fluconazole	0.06–0.5	2	0.12 to >128
Itraconazole	0.06–0.25	0.12–0.5	0. 015 to >8
Voriconazole	0.007–0.06	0.06–0.25	≤0.002 to >16
Candida parapsilosis			
Fluconazole	0.5–1.0	1.0–8	0.12–16
Itraconazole	0.06–0.25	0.12–0.5	≤0.015–2
Voriconazole	0.007–0.06	0.03–0.25	≤0.0002–1
Candida glabrata			
Fluconazole	4–16	8–64	0.25 to >128
Itraconazole	0.5–1	1–4	0.06 to >8
Voriconazole	0.06–1	0.25–2	0.004–8
Candida krusei			
Fluconazole	16–64	64 to >128	2 to ⩾128
Itraconazole	0.25–2	0.25–4	0.12 to >4
Voriconazole	0.12–0.5	0.5–2	0.015–2
C. albicans, fluconazole-resistant			
Fluconazole	32	⩾128	16 to ⩾128
Itraconazole	0.25	1	0.03–1
Voriconazole	0.25	1	0.015–8
Cryptococcus neoformans			
Fluconazole	2–4	8–16	0.125–16
Itraconazole	0.125–0.25	0.5–1	≤0.007–1
Voriconazole	0.06–0.25	0.12–0.25	≤0.007–2

NOTE. Data are from [3–9].

tomyces dermatitidis, Coccidioides immitis, and *Histoplasma capsulatum* but is less active against *Sporothrix schenckii* [9, 15]. A variety of dematiaceous and hyaline molds, many of which are resistant to amphotericin B, are susceptible to voriconazole in vitro. This includes some, but not all, strains of *Pseudallescheria boydii* and its asexual form, *Scedosporium apiospermum; Fusarium* species; *Paecilomyces* species; *Bipolaris* species; *Alternaria* species; and others [12, 14, 16, 17]. The zygomycetes are not susceptible to voriconazole [18].

PHARMACOLOGY

Voriconazole is available in both intravenous and oral formulations. The intravenous formulation is solubilized in sulfobutyl ether β-cyclodextrin sodium (SBECD) and is infused over 1–2 h. In adults, steady-state plasma levels after intravenous infusion of 3–6 mg/kg twice daily range from 3 to 6 μg/mL [19]. Steady-state concentrations are achieved only after 5–6 days, but, if a loading dose is given, steady-state concentrations are achieved within 1 day [20]. The recommended regimen is a loading dose of 6 mg/kg every 12 h for 2 doses, followed by a maintenance dose of 4 mg/kg every 12 h.

The oral formulation of voriconazole is available as 50-mg and 200-mg tablets. When administered either 1 h before or 1 h after a meal, the bioavailability of the oral formulation is >90%. Gastric acid is not needed for absorption; fatty foods decrease bioavailability to ~80%. In adults, after oral administration of 200 mg twice daily, steady-state plasma concentrations generally range from 2 to 3 μg/mL [21]. Patients who weigh >40 kg should receive 200 mg every 12 h, and those who

Table 2. In vitro susceptibilities of voriconazole compared with those of other antifungal agents that are active against common *Aspergillus* species and other molds.

Species, antimicrobial agent	MIC_{50} range or value, μg/mL	MIC_{90} range or value, μg/mL	MIC range, μg/mL
Aspergillus fumigatus			
Amphotericin B	0.25–1	0.5–4	0.125–8
Itraconazole	0.06–0.5	0.5–1.0	<0.03–32
Voriconazole	0.03–0.5	0.25–2	<0.03–4
Aspergillus flavus			
Amphotericin B	0.125–2	0.5–8	0.125–8
Itraconazole	0.25–0.5	0.25–1	0.125–16
Voriconazole	0.25–1	0.5–2	0.125–2
Aspergillus niger			
Amphotericin B	0.125–0.5	0.125–4	0.125–4
Itraconazole	0.25–1	0.5–4	0.06–8
Voriconazole	0.25–1	0.5–4	0.25–4
Aspergillus terreus			
Amphotericin B	8	4 to >16	0.5–32
Itraconazole	0.06	0.125–0.25	0.03–0.5
Voriconazole	0.5	1	0.25–2
Scedosporium apiospermum			
Amphotericin B	2–4	8 to >16	1 to >16
Itraconazole	8 to >16	4 to >16	.03 to >16
Voriconazole	0.25–1	0.25–2	0.01–2
Scedosporium prolificans			
Amphotericin B	8 to >16	⩾16	0.125 to >16
Itraconazole	⩾16	>16	8 to >16
Voriconazole	2–16	4–16	0.06–32
Fusarium solani			
Amphotericin B	1	2–4	0.5–4
Itraconazole	>16	>16	>16
Voriconazole	2	4 to >8	1 to >8

NOTE. Data are from [9–14, 16, 17].

weigh <40 kg should receive 100 mg every 12 h. Steady-state concentrations are achieved within 24 h if a loading dose twice the amount of the daily dosage is given on day 1.

In adults, voriconazole exhibits nonlinear pharmacokinetics, which is thought to be related to saturation of metabolism [20]. There is substantial intersubject variability in the serum concentrations achieved. In children, elimination is linear, and higher dosages are required to attain the serum concentrations noted in adults [22]. Voriconazole is 58% protein bound and has a large volume of distribution. In animals and humans, concentrations in the CSF are ~50% of plasma concentrations; concentrations in brain tissue are higher than those in the CSF. Less than 5% of the drug is excreted unchanged in the urine.

Metabolism of voriconazole occurs in the liver via the CYP450 enzyme family, including the CYP2C9, CYP3A4, and CYP2C19 isoenzymes. The metabolites do not have antifungal activity. The activity of the CYP2C19 pathway, which is the major metabolic pathway for voriconazole, is highly dependent on genetic characteristics; as many as 20% of non-Indian Asians have low CYP2C19 activity and can achieve voriconazole levels as much as 4 times higher than those noted in homozygous subjects who metabolize the drug more extensively. This "poor metabolizer" trait is uncommon in white and black populations worldwide. There are no dosage adjustments recommended with regard to this observation at this point in time. However, the observation that hepatic toxicity might be dose related should prompt careful attention to the monitoring of liver enzyme levels in this population. As might be predicted, drug-drug interactions (see the next section, below) are of major importance in the safe use of voriconazole.

Dosage adjustments are necessary for patients with liver dysfunction. The standard loading dose should be used but the maintenance dosage should be halved in patients with mild-to-moderate liver disease. No studies have evaluated the safety of voriconazole in patients with severe liver disease. No adjustment in the dosage of the oral formulation of voriconazole is necessary in patients with renal insufficiency. However, moderate renal insufficiency (creatinine clearance of 30–50 mL/min) results in accumulation of the intravenous vehicle SBECD, and, therefore, intravenous administration should be avoided for patients who have a creatinine clearance <50 mL/min.

DRUG-DRUG INTERACTIONS

The potential for drug interactions with voriconazole is high because of its metabolism by CYP450 isoenzymes (table 3) [19]. Inducers of CYP450, such as rifampin, long-acting barbiturates, and carbamazepine, decrease voriconazole concentrations, and use of these drugs in combination with voriconazole should be avoided. Rifabutin and voriconazole coadministration not only leads to decreased voriconazole levels but also increases rifabutin serum concentrations to toxic levels; concomitant use of these 2 agents is contraindicated. A similar 2-way interaction occurs between voriconazole and phenytoin, which is a CYP2C9 substrate and potent CYP450 inducer. Phenytoin decreases voriconazole levels; when the 2 drugs are given concomitantly, the dosage of voriconazole given orally should be doubled. However, voriconazole increases phenytoin levels by competing for the CYP2C9 enzyme by which phenytoin is metabolized. Thus, phenytoin levels must be monitored carefully when the 2 agents are used concomitantly.

Voriconazole also interferes with the metabolism of several other drugs through inhibition of either the CYP3A4 or the CYP2C9 pathway, and coadministration can lead to toxic levels of those other drugs. Sirolimus, ergot alkaloids, terfenidine, astemizole, quinidine, and cisapride are contraindicated when voriconazole is used because of the potential for life-threatening reactions. The effects of voriconazole on tacrolimus, cyclosporine, and warfarin have been studied [23, 24]; decreasing the dosages of these medications is necessary, along with very careful evaluation of serum levels of the drug or markers for the drug's activity (e.g., prothrombin time). Care should be taken with concomitant administration of voriconazole and statins, benzodiazepines, calcium channel blockers, sulfonylureas, proton pump inhibitors, or vinca alkaloids. In most cases, the dosage of the other drug should be decreased and/or markers for its activity carefully monitored, because inhibition of metabolism and increased serum levels are likely. Correspond-

Table 3. Drug interactions with voriconazole.

Type of interaction, drug	Recommendation
Decreases voriconazole levels	
Carbamazepine	Contraindicated
Long-acting barbiturates	Contraindicated
Rifampin	Contraindicated
Levels increased by voriconazole	
Astemizole	Contraindicated
Cisapride	Contraindicated
Cyclosporine	Reduce dosage by one-half and monitor levels
Ergot alkaloids	Contraindicated
Omeprazole	Reduce dosage by one-half
Quinidine	Contraindicated
Sirolimus	Contraindicated
Tacrolimus	Reduce dosage to one-third of its original level and monitor levels
Terfenadine	Contraindicated
Warfarin	Monitor prothrombin time
Decreases voriconazole levels and increases other drug levels	
Rifabutin	Contraindicated
Phenytoin	Double voriconazole dosage and monitor for increased phenytoin levels
Levels likely increased by voriconazole: sulfonylureas, statins, vinca alkaloids, calcium channel blockers, benzodiazepines	Monitor effects of drug and consider decreasing dosage when voriconazole is added

ingly, when voriconazole treatment is stopped, the dosages of these drugs will need to be increased. Drugs that do not require dosage adjustment include cimetidine, digoxin, indinavir, macrolides, mycophenolate, prednisolone, and ranitidine.

SIDE EFFECTS

Voriconazole is generally well tolerated. The most common side effect—one not previously noted with other azoles—is a reversible disturbance of vision (photopsia). This occurs in ~30% of patients but rarely leads to discontinuation of the drug [20–22, 25–27]. Visual disturbances include altered color discrimination, blurred vision, the appearance of bright spots and wavy lines, and photophobia. Symptoms tend to occur during the first week of therapy and decrease or disappear in spite of continued therapy in most patients. Patients whose therapy is initiated in an outpatient setting should be cautioned that driving may be hazardous because of the risk of visual disturbances. The visual effects are associated with changes in electroretinogram tracings, which revert to normal when treatment with the drug is stopped; no permanent damage to the retina has been noted.

Skin rashes are the second most common adverse effect noted with voriconazole therapy. Most of these are mild and constitute no major problem. However, severe reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in a very small number of patients. Patients should be warned to avoid direct sunlight, because photosensitivity reactions can occur. Five patients who developed facial erythema and cheilitis have been described; 1 of these patients also developed lesions similar to those characteristic of discoid lupus erythematosus [28]. All of these effects disappeared after voriconazole treatment was stopped, but a direct causal relationship was not clear for all 5 patients.

Elevations in hepatic enzyme levels occur with voriconazole therapy, as they do with other azole therapy. The usual pattern described has been elevations in the serum levels of alanine aminotransferase and aspartate aminotransferase, but elevations in alkaline phosphatase levels have also been noted. Although most patients have asymptomatic elevation of hepatic enzyme levels, several patients with severe life-threatening hepatitis have been described. The risk of developing hepatitis appears to increase with increased serum voriconazole levels [29] and resolves with discontinuation of treatment with the drug. Patients receiving voriconazole should have liver function tests performed prior to therapy, within the first 2 weeks after the initiation of therapy, and then every 2–4 weeks throughout therapy.

Other less commonly noted side effects include headache, nausea and vomiting, diarrhea, abdominal pain, and visual hallucinations. Visual hallucinations occurred at a rate of 5% in one clinical trial and clearly differed from photopsia [27].

CLINICAL USE

Aspergillosis. Voriconazole is approved for the treatment of invasive aspergillosis on the basis of the results of a large, multinational, randomized treatment trial that compared voriconazole with amphotericin B and the results of a smaller, European, open, noncomparative trial [30, 31]. The noncomparative trial enrolled 141 patients, 116 of whom were deemed evaluable; most patients had a hematological malignancy or had received an allogeneic stem cell transplant [30]. The study included patients who had received prior antifungal therapy for aspergillosis as well as those who received voriconazole as primary therapy. The overall rate of complete or partial responses was 48%. Of the 60 patients (52%) who received primary therapy with voriconazole, 59% had either a complete or a partial response; of the patients who received voriconazole as salvage therapy after failure or intolerance of other antifungal therapy, 38% had either a complete or a partial response. When compared with historical controls, the data from this trial showed that voriconazole therapy had equivalent or improved efficacy for some types of aspergillosis. However, a firm assessment of the role of voriconazole in the treatment of invasive aspergillosis could not be made because of the uncontrolled design of the study and the comparison with outcomes for patients treated 5–10 years earlier.

A subsequent large, randomized trial compared voriconazole with standard amphotericin B for primary treatment of invasive aspergillosis [31]. Case definitions for invasive aspergillosis were well defined, and outcomes were determined by an expert panel blinded to the drug that the patient had received. Physicians were allowed to switch a patient's therapy to another approved antifungal agent if the patient did not tolerate the drug he or she was initially randomized to receive. Not surprisingly, this was done far more frequently in the amphotericin B arm than the voriconazole arm. Of 277 patients who had confirmed invasive aspergillosis and who received $\geq$1 dose of study drug, 144 were randomized to receive voriconazole and 133 were randomized to receive amphotericin B. More than 80% of patients in both treatment groups had invasive pulmonary aspergillosis and had hematological malignancies or had received stem cell transplants. Complete or partial responses at week 12 were noted in 53% of patients in the voriconazole group and in 32% of patients in the amphotericin B group (difference, 21.2%; 95% CI, 10.4%–32.9%). The survival rate was 71% in the voriconazole group and 58% in the amphotericin B group ($P = .02$). These results showed voriconazole to be more ef-

fective than amphotericin B for primary treatment of patients with invasive aspergillosis.

Pseudallescheria/Scedosporium *infections.* Voriconazole is approved for treatment of infections due to *P. boydii* and its asexual form, *S. apiospermum,* in patients intolerant of or with infections refractory to other agents. These fungi, which are generally amphotericin B resistant, have emerged as major pathogens among immunocompromised hosts, especially allogeneic stem cell transplant recipients [32, 33]. The clinical experience with voriconazole treatment of scedosporiosis and pseudallescheriasis mirrors in vitro results, showing excellent activity against *S. apiospermum* but only modest activity against *Scedosporium prolificans,* an organism found mostly in Spain and Australia [16, 17]. In a series of 36 cases of *Scedosporium* infection in which voriconazole was used for salvage therapy, 63% of patients with *S. apiospermum* infections but only 29% of those with *S. prolificans* infections had a complete or partial response [34]. In one series, 5 of 6 children with *S. apiospermum* infections but 0 of 2 children with *S. prolificans* infections responded to therapy with voriconazole [22]. Individual case reports have noted successful outcomes for voriconazole treatment of *S. apiospermum* or *P. boydii* pulmonary, disseminated, and CNS infections [35–39].

Fusarium *infections.* Voriconazole is approved for the treatment of *Fusarium* infections in patients intolerant of or with infection refractory to other drugs. For *Fusarium* species, MICs of voriconazole are substantially lower than MICs of itraconazole, but they are higher than those noted for other molds [12–14]. Reports of the use of voriconazole therapy for *Fusarium* infections are limited [40]. A case of keratitis due to *Fusarium solani* was cured with surgery, topical voriconazole therapy, and 8 weeks of high-dose, orally administered voriconazole therapy [41]. In data presented to the FDA, 9 (43%) of 21 patients with fusariosis had a complete or partial response to voriconazole, which was provided on a compassionate-use basis.

NONLICENSED USES

Candida *infections.* A multicenter, randomized, double-blind, double-dummy study compared voriconazole with fluconazole for the treatment of esophageal candidiasis in 391 immunocompromised patients, most of whom had AIDS [26]. Patients received either voriconazole, 200 mg twice daily, or fluconazole, 200 mg daily, for at least 7 days (range, 2–6 weeks) after clinical resolution. There was no difference between the 2 groups with respect to cure, as determined by esophagoscopy (98.3% of patients who received voriconazole and 95.1% of patients who received fluconazole achieved cure). One small open-label, noncomparative study evaluated the efficacy of voriconazole treatment for fluconazole-refractory esophageal candidiasis in 12 patients with AIDS [42]. At day 7, six patients were cured, and the conditions of 3 showed marked improvement; 1 other patient was cured after 2 weeks of therapy, and, in 2 patients, there was no response. Thus, voriconazole treatment is efficacious for patients who have esophageal candidiasis, including some who have fluconazole-refractory disease. There are few available clinical data with regard to the treatment of other forms of candidiasis. A multinational, randomized, blinded trial comparing voriconazole with amphotericin B followed by fluconazole for the treatment of candidemia in nonneutropenic patients is still ongoing.

Empirical treatment of febrile neutropenic patients. The results of a large, multicenter, randomized study that compared voriconazole ($n = 415$) with liposomal amphotericin B ($n = 422$) for empirical treatment of febrile neutropenic patients have been controversial [27]. The voriconazole treatment group did not meet the predefined composite primary end point for noninferiority, compared with the liposomal amphotericin B group; the lower limit of the 95% CI was outside the margin allowed by 0.6%. When individual elements of the 5-element composite end point were evaluated, data for 4 of the 5 elements favored liposomal amphotericin B, but the differences were not statistically significant. Data for the fifth element, proven breakthrough fungal infection—which, many would argue, is the most important end point—favored voriconazole. Breakthrough fungal infections occurred in 8 patients (1.9%) in the voriconazole group compared with 21 patients (5%) in the liposomal amphotericin B group ($P = .02$). The number of deaths was similar in both groups. The FDA did not approve voriconazole for empirical treatment of febrile neutropenic patients because of the failure of the trial to meet the composite primary end point. This decision, as well as the design of the trial, has been questioned [43–45].

Cryptococcosis. Voriconazole demonstrates excellent in vitro activity against *C. neoformans* and achieves good CSF levels [7–9]. No clinical trial results and only a few case reports of voriconazole use against cryptococcal meningitis have been published [40]. In a report of a case of relapsing cryptococcal meningitis due to a fluconazole-resistant isolate in a patient with advanced HIV infection, maintenance therapy with voriconazole was unsuccessful at preventing a recurrence of meningitis [46]. At this time, voriconazole cannot be recommended for treatment of patients with cryptococcosis.

Endemic mycoses. Voriconazole is active in vitro against *B. dermatitidis, C. immitis,* and *H. capsulatum* [9, 15] and has been shown to be effective in an animal model of pulmonary blastomycosis [47]. There are no data available from clinical trials, and only a few cases noting that voriconazole is effective against infections caused by these fungi have been reported

[40]. At present, voriconazole cannot be recommended for treatment of endemic mycoses.

SUMMARY

Voriconazole is a second-generation triazole that is derived from fluconazole and that has an enhanced antifungal spectrum, compared with older triazoles. It will likely become the drug of choice for treatment of invasive aspergillosis and many *Scedosporium/Pseudallescheria* and *Fusarium* infections. Voriconazole should not replace fluconazole or other antifungal agents for treatment of most *Candida* infections. The drug has more side effects and drug interactions than fluconazole. The oral formulation, with its excellent bioavailability, can be used in patients with a functional gastrointestinal tract; it is especially beneficial in patients with renal failure, who should not be exposed to the cyclodextrin vehicle used for the intravenous formulation; and it is considerably cheaper than the intravenous formulation.

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