Voriconazole: A New Antifungal Agent

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The development of resistant candida and the emergence of other resistant organisms, such as Aspergillus, have negatively affected the success of commercially available antifungal agents. Azole antifungals, although previously effective, are subject to limitations, including a fungistatic mechanism of action and drug interactions. Although amphotericin is an effective agent, it carries high costs associated with its liposomal formulation and also raises concerns about its toxicity.

An increase in life-threatening invasive fungal infections in neutropenic and immunosuppressed patients has prompted scientists and clinicians to develop more effective alternatives. One focus of antifungal therapy research is the modification of existing azole compounds. In October 2001, an advisory panel to the Food and Drug Administration (FDA) recommended approval of voriconazole (Vfend, Pfizer) for serious fungal infections associated with its liposomal formulation and also raises concerns about its toxicity.

Voriconazole is distributed extensively from fluconazole because of the addition of a methyl group to the propyl backbone and the substitution of a triazole moiety with a fluoropyrimidine group. Azoles work primarily via inhibition of cytochrome P450-14α-demethylase, thereby inhibiting steps in the synthesis pathway for fungal membrane production and growth. Voriconazole interferes with both 14α-demethylase and 24-methylene dihydrolanosterol demethylation, which might explain its increased activity against certain molds.

Voriconazole’s structural differences increase its affinity for the 14α-sterol demethylase of aspergillus fumigatus beyond that of fluconazole. Whereas fluconazole has a 50% inhibitory concentration (IC50) of 4.8 μM for the 14α-sterol demethylase, voriconazole’s affinity for the enzyme was increased as the IC50 decreased to 0.48 μM. The pyrimidine moiety further increased voriconazole’s antifungal potency, giving it an IC50 of 0.053 μM. The 2R, 3S enantiomer was determined to be the more active of the diastereomer pair. As a result, voriconazole has a broader spectrum of activity and greater efficacy compared to fluconazole.

PHARMACOKINETICS

Initial pharmacokinetic data for normal human subjects show that voriconazole is well-absorbed after oral administration (90%), with maximum concentrations in serum reached within two hours. Voriconazole, like itraconazole, is metabolized by the liver and the metabolites are excreted in the bile and urine. There is also a disproportionate increase in serum concentrations with increased dosage, suggesting saturable first-pass metabolism in the liver. Voriconazole has a mean serum elimination half-life of about six hours, which is shorter than that for itraconazole or fluconazole. Steady-state serum concentrations are reached within five to seven days at a dose of 200 mg twice daily.

Klepser et al. employed in vitro time-kill methods to establish the relationship between voriconazole concentrations and its fungistatic activity compared to Candida albicans, Candida glabrata, Candida tropicalis and Candida neoformans. Isolates were exposed to voriconazole concentrations ranging from 0.0625 to 16 times the mean inhibitory concentration (MIC) and the viable colony counts were determined over time. The 50% and 90% effective concentrations (EC50 and EC90) were determined at eight, 12, and 24 hours following the addition of voriconazole. At each time point, near maximal fungistatic activity, as indicated by the EC90, was noted at a drug concentration of approximately three times that of the MIC. In addition, the EC50 and EC90 did not change over time, suggesting that the rate of activity was not improved by increasing concentrations. The authors concluded that voriconazole exhibits non-concentration-dependent activity in vitro.

Voriconazole is distributed extensively in humans, with a steady-state volume of distribution of 2L/kg. It is moderately bound to plasma protein (51%–67%), as reflected by saliva concentrations, about 65% of those in plasma. Specific plasma proteins to which the agent is bound have yet to be determined. There is scarce data on the drug’s distribution in the extravascular tissue.

Voriconazole undergoes hepatic metabolism through the cytochrome P450 (CYP-450) enzyme system. Currently, eight metabolites have been described, of which three are major metabolites and five are minor metabolites.

Although voriconazole has an elimination half-life of six hours, six days are needed to recover 90% of the drug in the urine and feces of patients receiving lengthy courses of treatment. The metabolites are eliminated primarily through urinary excretion; however, the
time to elimination has yet to be established. Less than 5% of the parent compound has been found in the urine.6

EFFICACY
Voriconazole’s efficacy in fluconazole-resistant oropharyngeal candidiasis was evaluated by Hegener et al.8 Twelve HIV-positive patients ranging from 26 to 29 years of age and having endoscopically confirmed oropharyngeal candidiasis were enrolled. All infections were resistant to fluconazole. Oral voriconazole was started at 200 mg twice daily and efficacy was subsequently assessed weekly. Positive clinical responses were defined by significant improvement (complete and partial response), and mycologic response was defined by disappearance of the organism on culture. Ten patients (83%) responded positively to treatment. Six patients had complete response in seven days; three patients improved in seven days; and one patient had a complete response in 14 days. The remaining two patients remained clinically unchanged. The overall duration of clinical response was highly variable, between one and 40 weeks.

In a case study by de Sevaux et al.,9 a 30-year-old male patient colonized with Aspergillus fumigatus in the bronchioles was successfully cured using voriconazole 200 mg twice a day. Radiologic abnormalities diminished after two weeks and disappeared within three months. Hilmarsdóttir et al.10 reported a case of cutaneous Paecilomyces lilacinus on the toes and dorsum of the right foot of a 59-year-old man. After failing oral itraconazole therapy, voriconazole was started 200 mg twice a day orally. The infection began to improve, and after six weeks, the lesions had healed and swelling and erythema had decreased. Although the patient expired because of subsequent complications, the authors concluded that voriconazole was a benefit in treating Paecilomyces.

The in vitro antifungal activity of voriconazole was compared with those of itraconazole and amphotericin B against 67 isolates of Aspergillus flavus, Aspergillus fumigatus, Bipolaris spp., Fusarium oxysporum, Fusarium solani, Pseudallescheria boydii (P. boydii), Rhizopus arrhizus, Blastomyces dermatisid, Histoplasma capsulatum, and Sporothrix schenckii. The in vitro activities of voriconazole were also compared with those of amphotericin B, fluconazole, and itraconazole against 189 isolates of emerging and common yeast pathogens. The activities of voriconazole were similar to or better than those of itraconazole and amphotericin B against Aspergillus spp., Fusarium spp., and P. boydii. The activities of voriconazole were also comparable to or better than those of amphotericin B, fluconazole, and itraconazole against most species of yeast tested.11

The in vitro susceptibility of a large number of clinical and laboratory isolates of Aspergillus was evaluated by Abraham et al.12 Voriconazole exhibited excellent activity against all aspergillus species in concentrations significantly lower than that of amphotericin B. Against Aspergillus fumigatus, itraconazole had significantly better activity than voriconazole. No significant difference was noted in the MIC of voriconazole and itraconazole for other Aspergillus strains evaluated. Voriconazole lacked cross-resistance with itraconazole. Based on the potent in vitro activity, voriconazole was found to be an effective agent.

ADVERSE REACTIONS
Increased brightness and blurred vision are the most frequently reported voriconazole toxicities, followed by increased liver enzymes. Another less frequently reported side effect was skin rash.13 One case report suggested a possible relationship between voriconazole and photosensitivity, with skin lesions developing after exposure to strong sunlight.14 Some evidence suggests voriconazole might not possess the ability to change serum hormone concentrations, which is seen with ketoconazole, although this has yet to be elucidated in vivo. This might decrease the potential for a lesser effect on the inhibition of sterol biosynthesis. Ketoconazole appears to be the most potent azole to inhibit mammalian 14-α-sterol demethylase, with an IC₅₀ for voriconazole, itraconazole, and ketoconazole of 8, 2.3, and 1.4 µM, respectively. The data suggest that voriconazole might interact to a lesser degree with CYP-450 enzymes accountable for the metabolism of steroid hormones.15

PRECAUTIONS AND CONTRAINDICATIONS
Currently, no contraindications or precautions are clearly established. Because of elevations in liver-function tests, patients with hepatic impairment should be cautioned. Because visual disturbances have been reported, those with disorders of the eye should also be cautioned.

PREGNANCY AND LACTATION
There are no data available regarding the use of voriconazole in pregnant patients or whether the compound and metabolites are excreted into breast milk.

DRUG INTERACTIONS
There is no information regarding drug–drug interactions with voriconazole. Like fluconazole, voriconazole is metabolized by the hepatic CYP-450 enzyme system and might be prone to many of the same drug interactions observed with the other azole agents. The likelihood of CYP2C9 and CYP3A4 involvement is relevant. Because information is limited, caution should be maintained while co-administering substrates of the same system3. Some of these agents include phenytoin, rifampin, cyclosporine, and warfarin. Also, drug–food interaction data have not been elucidated. Just as currently availableazole antifungals interact with grapefruit juice, voriconazole might be subject to bio-transformation as well. Further evaluation is required.

CONCLUSION
Voriconazole will be used to target serious fungal infections in patients refractory to other azoles or amphotericin. Also, it might be used in patients who cannot tolerate amphotericin. Because the manufacturer will be distributing both oral and intravenous preparations, treatment decisions regarding administration might be
less complicated. Although the data are limited, it appears that voriconazole can offer a significant alternative to other antifungal agents with a limited spectrum of activity, lack of a convenient dosage form, or patient intolerance. Limited data suggest that voriconazole exhibits a favorable kinetic and safety profile that might be similar to the existing azole antifungals. Although resistance has not yet been documented, it might exist, despite the relatively lower MICs for voriconazole. Overall, voriconazole appears to be a potentially viable agent against fungal pathogens.

REFERENCES