Drug Therapy

Voriconazole

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Voriconazole (VRZ) is a second-generation triazole antifungal agent active against many species of Aspergillus and Candida and acts by inhibiting ergosterol synthesis. VRZ has less nephrotoxicity and less infusion-related toxicity than that of Amphotericin B. Oral and parentral formulation have similar pharmacokinetics and thus oral formulation shortens the duration of hospital stay. It is overall well tolerated but has significant drug interactions.

Key words: *Aspergillosis, Candida, Voriconazole.*

Invasive fungal infections are a major cause of morbidity and mortality in patients with immunodeficiency states, HIV, immunosuppressive drugs, premature infants, hematologic conditions and oncologic diseases(1). Newer antifungal agents have been less toxic and in some cases have better efficacy than amphotericin B deoxycholate (ABD), which was the gold standard of anti-fungal treatment for years.

Voriconazole (VRZ) is a second-generation triazole antifungal agent approved by FDA in May 2002. VRZ is a synthetic derivative of fluconazole. Replacement of one of the triazole rings with a fluorinated pyrimidine and the addition of α-methyl group resulted in expanded activity, compared with that of fluconazole(1-3).

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Mechanism of Action

VRZ inhibits cytochrome P450 (CYP 450) dependent 14 α-lanosterol demethylation, which is a vital step in cell membrane ergosterol synthesis by fungi(4). For yeasts, VRZ appears to be fungistatic however, for some filamentous organisms it is fungicidal(5). This effect may relate to the stronger avidity for lanosterol 14α-demethylase found in molds, which may allow more complete interruption of ergosterol synthesis(3,5).

Pharmacokinetics

Pharmacokinetics of VRZ is similar following administration by IV or oral route. When administered either 1 h before or 1 h after a meal, the bioavailability of oral formulation is 96%. Gastric acid is not needed for absorption; fatty foods decrease bioavailability to approximately 80%. In adults, after oral administration of 200 mg twice daily, steady-state plasma concentrations generally range from 2-3 μg/mL(6). In adults, steady-state plasma levels after intravenous infusion of 3-6 mg/kg twice-daily ranges from 3 to 6 μg/mL. 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 (7). On increasing the oral maintenance dose by 50% or IV maintenance dose by 25%, there is 2.5 fold or 2.3 fold increase in exposure *i.e.*, area under curve(1-3,6,7).

In adults, VRZ exhibits nonlinear

pharmacokinetics, which is probably related to saturation of metabolism(7). In children, elimination is linear, and higher dosages are required to attain the serum concentrations noted in adults(8). VRZ is 58% protein bound and has a large volume of distribution. Concentrations in 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 (1-3,9,10).

VRZ is metabolized in the liver via the CYP450 enzyme family. 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 VRZ in patients with severe liver disease. No dose adjustment of oral VRZ is necessary in renal insufficiency. However, moderate renal insufficiency (creatinine clearance of 30-50 mL/min) results in accumulation of the intravenous vehicle SBECD, and, therefore, IV administration should be avoided for these patients (2,3,9,10).

Antifungal spectrum

VRZ appears to be broadly active against many species of Aspergillus, including *Aspergillus terreus*, which is often resistant to amphotericin B (AmB) (5,11-12). *Table I* shows the Antifungal spectrum. VRZ 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(5,13).

Therapeutic uses

Aspergillosis (FDA approved)

VRZ is approved for the treatment of invasive aspergillosis on the basis of the results of a large, multinational, randomized treatment trial that compared VRZ with AmB and the results of a smaller, European, open, noncomparative trial(9,10). First-line treatment options for invasive aspergillosis include VRZ or AmB preparations.

Pseudallescheria/Scedosporium and Fusarium infections (FDA approved)

VRZ 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 AmB resistant, have emerged as major pathogens among immunocompromised hosts (14).

Candidiasis (FDA approved)

VRZ treatment is efficacious for patients who have esophageal candidiasis including some who have fluconazole-refractory disease(15-16).

Febrile Neutropenia (Institutional Recommendation)

The FDA has not approved VRZ for empirical treatment of febrile neutropenic patients. AmB is the first-line treatment for febrile neutropenia unresponsive to broad-spectrum antibiotic therapy; VRZ is considered an appropriate alternative choice by many authorities(2,16-18).

Place of VRZ in therapy

VRZ will find a place in treating documented fungal infections where resistance is suspected or in cases of failure of first line drugs. It has a role in conditions of renal dysfunction or administration of concurrent nephrotoxic drugs. VRZ has less nephrotoxicity and less infusion-related toxicity than that of Am B, which increase the cost of treatment considerably. This nephrotoxicity with AmB is clinically significant, especially in the most heavily

TABLE I–*Comparison of Fluconazole, Voriconazole and Amphotericin B.*

	Fluconazole	Voriconazole	Amphotericin B
Spectrum of activity	*Candida albican*s, Cryptococcosis, histoplasmosis, blastomycosis, sporotrichosis,	*Candida albicans*, *Candida* krusei, *Candida glabrata*, *Aspergillus*, *Cryptococcus neoformans*, *Histoplasma* capsulatum, Coccidioides immitis,; Blastomyces dermatitidis, Trichosporon beigelii, and Saccharomyces *cerevisiae*	Candida spp, Aspergillus spp, *Cryptococcus neoformans, Histoplasma capsulatum, Mucormycosis*, *Coccidioides immitis*, *Sporothrix schenki*i, *Paracoccidioides* braziliensis, Penicillium *marneffei*
Frequency of administration	Once daily	Twice daily	Once daily
Oral bioavailability	100 %	96 %	Nil
Specific indication	Candidiasis, cryptococcosis, coccidioidal meningitis	Aspergillosis, Pseudallescheria/Scedosporium and Fusarium infections, Candidiasis, Febrile Neutropenia	Invasive aspergillosis, mucormycosis, extracutaneous sporotrichosis, cryptococcosis, fusariosis, coccidioidal meningitis, febrile neutropenia
Adverse effects	Nausea, vomiting, headache, skin rash, reversible alopecia, Stevens Johnson syndrome	Visual disturbances Skin rashes headache, nausea and vomiting, diarrhea, abdominal pain, and visual hallucinations, elevated transaminases	Fever and chills, phlebitis, headache, nausea and vomiting, malaise, weight loss, tachypnea, hypotension, thrombocytopenia
Renal disease	None significant	None significant	Hypokalemia, azotemia, renal tubular acidosis,
Cost (Rs/day)[#]	35	1600, 2800*	300, 3500,10,000[+]

[#] Full adult dose; * Different company prices; [+] Conventional, AmB Lipid complex, liposomal AmB respectively.

immunosuppressed patients who are exposed to multiple drugs(2). A benefit of VRZ compared with AmB on patient survival was seen at day 84 with 71% survival rate on VRZ compared to 58% with AmB(3). Availability of oral formulation makes a switchover from intravenous to oral route easy and subsequent early discharge will also reduce the treatment cost. *Table I* compares spectrum and activity of fluconazole, voriconazole and amphotericin B. VRZ is not effective against mucomycosis.

Adverse reactions

VRZ is generally well tolerated. The most common side effect is a reversible disturbance of vision (photopsia) if drug is used beyond 28 days. This occurs in 30% of patients but rarely leads to discontinuation of the drug (6-8,19). 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. 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 but are mild. Elevations in the serum levels of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase have been noted. Other less commonly noted side effects include headache, nausea and vomiting, diarrhea, abdominal pain, and visual hallucinations (1-3,6-9,19).

Precautions

VRZ should be taken 1 hr before or after a meal. Patients should not drive at night or operate machinery if they perceive changes in vision. They should also avoid direct sunlight during therapy. VRZ tablets contain lactose and should therefore be avoided in lactose or galactose intolerance(3). In preexisting mild to moderate liver dysfunction the full loading dose should be given. However, the maintenance dose should be reduced to half. Discontinuation of VRZ must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to VRZ. Moderate renal insufficiency (creatinine clearance of 30-50 mL/min) results in assumulation of the intravenous vehicle SBECD and therefore, IV administration should be avoided for these patients(2,3,9,10). In an overdose, the drug should be removed by hemodialysis(1-3, 6-9).

Contraindications

VRZ is contraindicated in patients with known hypersensivity to VRZ or to any of the excipients. Coadministration of VRZ with rifampicin, carbamazepine and long acting barbiturates (Phenobarbital) is contraindicated since these are likely to decrease plasma VRZ concentration significantly. Concurrent administration of cisapride is contraindicated as it may lead to QT prolongation and occurrences of torsades de pointes(3).

Drug interactions

Table II shows various drug interactions with VRZ. The following drugs do not require dosage adjustments: cimetidine, digoxin, indinavir, macrolide, mycophenolate, prednisolone, and ranitidine(2,3,9,20).

Doses and Administration

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. Patients who weigh >40 kg should

TABLE II–*Drug Interactions with Voriconazole*

Drug interaction	Recommendation
Decreases VRZ levels	
Carbamazapine	Contraindicated
Barbiturates	Contraindicated
Rifampin	Contraindicated
Increases VRZ levels	
Cisapride	Contraindicated
Cyclosporine	Reduce dose by half
Omeprazole	Reduce dose by half
Quinidine	Contraindicated
Warfarin	Monitor prothrombin time
Terfenadine	Contraindicated
Decreases VRZ levels and increases other drug levels	
Rifabutin	Contraindicated
Phenytoin	Double VRZ dose and reduce phenytoin by half-monitor phenytoin levels
Less likely increased by VRZ	
Vinca alkaloids, calcium channel blockers, benzodiazepines	Monitor drug effects and consider decreasing dose when VRZ is added

Key Messages

- Voriconazole is active against many species of Aspergillus and Candida.
- It has favorable pharmacokinetic and side effect profile.
- VRZ has less nephrotoxicity and less infusion-related toxicity than Am B, which makes it cost effective.

receive 200 mg every 12 h, and those who 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. Patients who are unable to tolerate treatment, reduce the IV maintenance to 3 mg/kg 12 hourly and the oral dose to reduce by 50 mg/day to a minimum of 200 mg every 12 hourly (or to 100 mg every 12 hourly in persons weighing <40kg). If response to treatment is inadequate then oral maintenance dose may be increased by 50%. VRZ is not recommended in children less than 2 years as the data regarding safety and effectiveness in this age group has not been established. VRZ must be infused over 1-2 hours at a concentration of 5 mg/ml or less at a maximum rate of 3mg/kg/hr. Infusion of blood products and any electrolyte supplementation must not occur simultaneously with VRZ infusion(2-3).

Formulations and cost

VRZ is available in both intravenous and oral formulations. The intravenous formulation vial contains 20 mg VRZ equivalent to a 10mg/ml solution following reconstitution. Reconstituted concentrate should be kept at 2-8ºC upto 24 hours in refrigerator. The oral formulation of VRZ is available as 50 mg and 200 mg film coated tablets. Tablets and powder for injection should be stored at controlled room temperature of 15-30ºC(3).

The cost of full adult dose is Rs 2800/day for Vfend (Pfizer) and Rs 1600/day for Voraze (Sun pharma).

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REFERENCES

1. Abuhammour W, Habte-Gaber E. Newer antifungal agents. Indian J Pediatr 2004; 71: 253-259.
2. Johnson LB, Kauffman CA. Voriconazole: A New Triazole Antifungal Agent. Clin Infect Dis 2003; 36: 630-637.
3. Voriconazole. *In:* Burnham TH, Novak KK, Short RM, Bell WL, Schwain SL, Harmen LD, editors. Drugs Facts And Comparisons. 57th ed. St. Louis: Facts& Comparisons; 2003. p 1505-1510.
4. Sanati H, Belanger P, Fratti B, Ghannoum M. A new triazole, voriconazole (UK-109, 496), blocks sterol biosynthesis in *Candida albicans* and *Candida krusei*. Antimicrob Agents Chemother 1997; 41: 2492-2496.
5. Manavathu EK, Cutright JL, Chandrasekar PH. Organism-dependant fungicidal activities of azoles. Antimicrob Agents Chemother 1998; 42: 3018-3021.
6. Lazarus HM, Blumer JL, Yanovicjh S, Schlamm H, Romero A. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: A dose escalation study. J Clin Pharmacol 2002; 42: 395-402.
7. Purkins L, Wood N, Ghahramani P, Greenhalgh

K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous-to oral-dose escalation regimens. Antimicrob Agents Chemother 2002; 46: 2546-2553.

8. Walsh TJ, Lutsar I, Driscoll T, Dupont B, Roden M, Ghahramani P *et al.* Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. Pediatr Infect Dis J 2002; 21: 240-248.

9. Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E *et al.* Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002; 34: 563-571.

10. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347: 408-415.

11. Oakley KL, Moore CB, Denning DW. In vitro activity of voriconazole against Aspergillus spp. and comparison with itraconazole and amphotericin B. J Antimicrob Chemother 1998; 42: 91-94.

12. Espinel-Ingroff A. *In vitro* fungicidal activities of voriconazole, itraconazole, and amphotericin B against opportunistic moniliaceous and dematiaceous fungi. J Clin Microbiol 2001; 39: 954-958.

13. Pfaller MA, Diekema DJ, Jones RN, Sader HS, Fluit AC, Hollis RJ *et al.* International surveillance of bloodstream infections due to Candida species: frequency of occurrence and *in vitro* susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. J Clin Microbiol 2001; 39: 3254-3259.

14. Revankar SG, Patterson JE, Sutton DA, Pullen R, Rinaldi MG. Disseminated phaeohyphomycosis: review of an emerging mycosis. Clin Infect Dis 2002; 34: 467-476.

15. Ally R, Schurmann D, Kreisel W, Carosi G, Aguirrebengoa K, Dupont B *et al.* A randomized, double blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infect Dis 2001; 33:1447-1454.

16. Hegener P, Troke P, Fatkenheuer G, Diehl V, Ruhnke M. Treatment of fluconazole-resistant candidiasis with voriconazole in patients with AIDS. AIDS 1998; 12: 2227-2228.

17. Powers JH, Dixon CA, Goldberger MJ. Voriconazole versus liposomal amphotericin B in patients with neutropenia and persistent fever [letter]. N Engl J Med 2002; 346: 289-290.

18. Walsh TJ, Lee J, Dismukes WE. Decisions about voriconazole versus liposomal amphotericin B [letter]. N Engl J Med 2002; 346: 1499.

19. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002; 346: 225-234.

20. Hoffman HL, Rathbun RC. Review of the safety and efficacy of voriconazole. Expert Opin Investig Drugs 2002; 11: 409-429.