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**Review Article**

# Safety of voriconazole in treatment of fungal infections

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## ABSTRACT

Immunocompromised patients are at more risk in developing fungal infections particularly with *Candida* and *Aspergillus* species being the mycoses most commonly identified. Previously, amphotericin-B is the drug of choice for the treatment of systemic infections caused by *Candida* and *Aspergillus* species. Due to its high incidence of toxicity, its use has been limited in many cases. Voriconazole is the newest triazole synthesized against fungal infections and was approved by FDA in 2002 for the treatment of invasive aspergillosis and refractory infections of *Scedosporium apiospermum* and *Fusarium* spp.

**Keywords:** Voriconazole, Antifungal agent, Safety

## INTRODUCTION

Invasive fungal infections (IFIs) are very common in immunocompromised patients and are responsible for significant morbidity and mortality.[1,2] Empirical antifungal therapy is usually prescribed to treat IFIs.[3] Amphotericin B is the gold standard anti-fungal agent prescribed for treating IFIs. But its use is very limited now-a-days due to its severe side effects such as electrolyte disturbances and nephrotoxicity.[4,5]

Many antifungal agents are available during the past 25 years with broad spectrum antifungal activity. Voriconazole is one of the second generation synthetic triazole with broad spectrum antifungal activity and is available in oral and intravenous formulations.[1] It is very effective and alternative for prophylaxis and treatment of mycotic infections in immunodeficient critically ill patients and in patients who are at high risk of developing IFIs.[6-8]

### *Mechanism of action*

Voriconazole binds and inhibits ergosterol synthesis by inhibiting fungal cytochrome P450 mediated 14-alpha lanosterol demethylation. This results in the structural damage and loss of cell membrane function.[9] In addition to the antifungal activity, voriconazole also specifically induces the expression of toll-like receptor 2, nuclear factor-κB, and tumor necrosis factor alpha in monocytes.[10]

### *Therapeutic indications*

Voriconazole is used as a first line treatment for invasive aspergillosis and invasive *Scedosporium* spp. and *Fusarium* spp. infections. The drug is used for treating candidiasis in non-neutropenic patients, fluconazole-resistant severe invasive candida infections (including *C. krusei*).[11,12] It can be used in different species of *Aspergillus* (*A. flavus, A. fumigatus, A. terreus, A. niger, A. nidulans*), *Fusarium, Scedosporium, Cryptococcus*

*neoformans, Alternaria, Penicillium, Blastomyces dermatidis, Cladosporium, Blastoschizomyces capitatus, Coccidioides immitis, Madurella mycetomatis, Exserohilum rostratum, Exophiala spinifera, Conidiobolus coronatus, Fonsecaea pedrosoi, Paecilomyces lilacinus, Phialophora richardsiae, Scopulariopsis brevicaulis*, and *Trichosporon* infections. It showed a greater activity against most molds compared with amphotericin B.[13-17] The drug can be used in children (above 2 years) and in adults. It can be used in pregnant women when the benefits to the mother outweigh the risk for the foetus. It is contraindicated during lactation.[18]

Voriconazole is available on the market in the form of film-coated tablets, oral suspension and as an infusion. It should be given 1 hour before meals.[12] Hypersensitivity reaction may be seen for the drug itself or other azoles. During the treatment regular monitoring of liver and kidney biochemical parameters should be done. Prolonged exposure to the sun should be avoided as photosensitivity usually develops with the drug after 12 weeks of management.[11]

### *Safety of voriconazole*

Voriconazole's safety has been evaluated in healthy volunteers and in patients throughout phase-1 and clinical trials.[19,20] The drug is generally well tolerated. Commonly reported adverse effects are visual disturbances, hepatic abnormalities, nausea, vomiting, fever, rashes, abdominal pain and headache.[21]

Visual abnormalities were noticed approximately in 30% of patients in clinical trials which include altered or enhanced visual perception, change in color vision, blurred vision and photophobia.[19,20] Patients with higher doses of drug or with high plasma concentrations may be more likely to experience visual abnormalities. Actual mechanism of visual disturbances is unknown. These disturbances were generally mild in nature usually experienced during first of therapy and were reversible after the discontinuation therapy. In a study done on healthy volunteers receiving voriconazole, disturbed retinal function was observed after 28 days of therapy.[19] The study found that voriconazole caused abnormalities on both the retinal rods and cones. Electroretinogram waveform amplitude and visual field were declined and changes in color perception was observed. After 14 days of treatment discontinuation, electroretinogram, visual fields and color perception had returned to baseline in most of the subjects.[19,20,22]

Deviations in hepatic transaminase levels was observed in 13.4% patients in clinical trials. Hepatic transaminases and alkaline phosphatase levels are increased more than 3 times the normal values in patients receiving voriconazole. These abnormalities have been associated with higher doses of the drug. The transaminase levels are returned to baseline after discontinuation of the drug.[19,20,22]

Skin reactions associated to voriconazole was noticed in approximately 6% of the patients in clinical trails. Most of them were mild to moderate and did not require treatment discontinuation. Severity and presentation of the skin reaction varies from one patient to the other particularly who were receiving steroids, antihistamines and other immunosuppressants. Four rare cases were reported of developing serious cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme) when receiving voriconazole. The patients using voriconazole should be monitored closely and should be discontinued if the reaction increases in severity.[19,20,22]

Marks et al in his study found that voriconazole was effective as prophylactic agent after allogeneic bone marrow transplantation and can be given for a significantly longer period, with less need of other systemic antifungals.[23]

Voriconazole was found to be safe and well tolerated as prophylactic in AML patients undergoing induction chemotherapy and noted a reduced incidence of lung infiltrates and hepatosplenic candidiasis.[24]

### *Drug interactions*

Voriconazole effects the metabolism of many drugs and vice versa. Use of voriconazole is contraindicated in patients receiving CYP3A4 substrates which may lead to QT prolongation (astemizole, terfenadine, cisapride, pimozide, quinidine). The drug increases the action of oral anticoagulants. It also increases the serum levels of tacrolimus and cyclosporine A, hence reduction of the dose of the drugs when given in combination is recommended. Monitoring of blood glucose levels is recommended during co-administration with sulphonylureas. Along with statins the voriconazole may lead to rhabdomyolysis, with benzodiazepines sedative action is prolonged and with vincristine and vinblastine can result in neurotoxicity.[14,18,25]

Coadministration of voriconazole along with enzyme inducers such as rifampicin, rifabutin, carbamazepine, efavirenz, nevirapine, ritonavir, amprenavir, barbiturates such as phenobarbital, pentobarbital, secobarbital, butabarbital decreases serum levels of voriconazole. Enzyme inhibitors such as cimetidine, omeprazole, oral contraceptives and fluconazole increases the levels of voriconazole. Hence, there is a need to increase triazole maintenance dose when the above drugs are given along with voriconazole.[18,25]

## CONCLUSION

Voriconazole can be considered as an effective triazole and the treatment of choice for invasive aspergillosis,

scedosporiosis and fusariosis but cannot be recommended over other antifungals for most candidal infections. Dose of the drug should be maintained when given in combination with enzyme inducers or inhibitors.

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## REFERENCES

1. Pearson MM, Rogers PD, Cleary JD, Chapman SW. Voriconazole: a new triazole antifungal agent. ANN Pharmacother. 2003;37:420-32.
2. Bes DF, Rosanova MT, Sberna N, Arrizurieta E. Deoxycholate amphotericin B nad nephrotoxicity in the pediatric setting. Pediatr Infect Dis J. 2014;33:198-206.
3. Xing Y, Chen L, Feng Y, Zhou Y, Zhai Y, Lu J. Meta-analysis of the safety of voriconazole in definitive, empirical, and prophylactic therapies for invasive fungal infections. BMC Infect Dis. 2017;17(1):798.
4. Shang W, Feng G, Sun R, Wang X, Liu W, Zhang S, et al. Comparison of micafungin and voriconazole in the treatment of invasive fungal infections in kidney transplant recipient. J Clin Pharm Ther. 2012;37:652-56.
5. Cornely OA, Ullmann AJ, Karthaus M. Evidence-based assessment of primary antifungal prophylaxis in patients with hematologic malignancies. Blood. 2003;101:3365-72.
6. Michael C, Bierbach U, Frenzel K, Lange T, Basara N, Niederwieser D, et al. Voriconazole pharmacokinetics and safety in immunocompromised children compared to adult patients. Antimicrob Agents Chemother. 2010;54:3225-32.
7. Potter M, Donnelly JP. The role of itraconazole in preventing and treating systemic fungal infections in immunocompromised patients. Acta Haematol. 2004;111:175-80.
8. Doring M, Blume O, Haufe S, Hartmann U, Kimmig A, Schwarze CP, et al. Comparison of itraconazole, voriconazole, and posaconazole as oral antifungal prophylaxis in pediatric patients following allogeneic hematopoietic stem cell transplantation. Eur J Clin Microbiol Infect Dis. 2014;33:629-38.
9. Sienkiewicz BM, Łapiński Ł, Wiela-Hojeńska A. Comparison of clinical pharmacology of voriconazole and posaconazole. Contemp Oncol (Pozn). 2016;20(5):365-73.
10. Ben-Ami R, Lewis RE, Kontoyiannis DP. Immunocompromised hosts: immunopharmacology of modern antifungals. Clin Infect Dis. 2008;47:226-35.
11. Adamski Z. Nowości i przyszłość w terapii przeciwgrzybiczej. Mikol Lek. 2005;12:115-21.
12. Sandherr M, Maschmeyer G. Pharmacology and metabolism of voriconazole and Posaconazole in the treatment of invasive aspergillosis: review of the literature. Eur J Med Res. 2011;16:139-44.
13. Lewis RE. Current concepts in antifungal pharmacology. Mayo Clin Proc. 2011;86:805-17.
14. Passowicz-Muszyńska E, Jankowska R, Weryńska B. Nowe leki przeciwgrzybicze stosowane w terapii grzybic głębokich. Mikol Lek. 2007;14:137-41.
15. Grudzień M, Pałka K, Pluciński F, Mazurek A. Molecular proprerties impact on bioavailability of second generation triazoles antifungal agents. Acta Pol Pharm. 2013;70:869-72.
16. Morris A. Review: Voriconazole for prevention or treatment of invasive fungal infections in cancer with neutropenia. ACP J Club. 2014;161:8.
17. Szymankiewicz M, Dancewicz M. Aktywność in vitro worikonazolu i kaspofunginy wobec szczepow Candida spp. oceniana metodą E-testu. Mikol Lek. 2008;15:13-5.
18. Aneks i charakterystyka produktu leczniczego VFEND, data zatwier-dzenia. 2012.
19. VFEND (voriconazole) tablets and injection [package insert] New York: Pfizer, Inc; 2002.
20. Pfizer Global Research and Development. Background document for the Antiviral Drug Products Advisory Committee meeting Oc tober 4, 2001: voriconazole tablets and voriconazole injection, Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_02_FDA-voriconazole.pdf. Accessed on 20 September 2002.
21. Greer ND. Voriconazole: the newest triazole antifungal agent. Proc (Bayl Univ Med Cent). 2003;16(2):241-8.
22. Florea NR, Kuti JL, Quintiliani R. Voriconazole: a novel azole an-tifungal. Formulary. 2002;37:389-99.
23. Marks DI, Pagliuca A, Kibbler CC, Glasmacher A, Heussel CP, Kantecki M, et al. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. Br J Hematol. 2011;155:318-27.
24. Vehreschild JJ, B€ohme A, Buchheidt D, et al. A double-blind trial on prophylactic voriconazole (VRC) or placebo during induction chemotherapy for acute myelogenous leukaemia (AML). J Infect. 2007;55:445-9.
25. Andes D, Pascua A, Marchetti O. Antifungal therapeutic drug monitoring: Established and emerging indications. Antimicrob Agents Chemother. 2009;53:24-34.

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