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REVIEW

Pharmacotherapy of Invasive Fungal Infections with Voriconazole

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Abstract: Voriconazole, a second-generation and broad-spectrum triazole derivative of fluconazole, inhibits the cytochrome P450 (CYP)-dependent enzyme 14-α-sterol demethylase, which is a pivotal step in cell membrane ergosterol synthesis in fungi. CYP2C19, CYP3A4, flavin-containing monooxygenase (FMO), and to a lesser extent CYP2C9 contribute to the oxidative metabolism of voriconazole by human liver microsomes. Clinical trials have demonstrated the safety and efficacy of voriconazole for prophylaxis and treatment in candidiasis, invasive aspergillosis, and in invasive fungal infections (IFIs) caused by a variety of non-*Aspergillus* molds, such as *Fusarium* or *Scedosporium* spp., and was generally well tolerated as primary therapy in adults and children. The availability of both parenteral and oral formulations and the nearly complete absorption (bioavailability of 96% for adults, ca. 40% in children) of the drug after oral administration provide for ease of use and potential cost savings, and ensure that the therapeutic plasma concentrations are maintained when switching from intravenous to oral regimes. It exhibits nonlinear pharmacokinetics in healthy controls and patients at high risk of IFIs, but considerable intra- and interpatient pharmacokinetic variability has raised the question of therapeutic drug monitoring. Most common adverse events are visual disturbances and elevated transaminase levels. The emergence of resistance towards voriconazole has been rarely reported.

Keywords: voriconazole, invasive fungal infections, drug interactions, adults, pediatrics, gender

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Introduction

Over the last two to three decades, an increase in the frequency and severity of invasive fungal infections (IFI) has been observed as a result of advances in the management of cancer, transplants and autoimmune diseases. Most are caused by *Candida* spp. and *Aspergillus fumigatus*. However, previously uncommon or new pathogens, many of which are resistant to antifungal agents, are increasing; these include non-fumigatus *Aspergillus* spp., *Scedosporium* and *Fusarium* spp.[1–7] Despite antifungal therapy, these IFIs imply an elevated rate of morbidity and mortality, with a mortality rate in high-risk patients of approximately 30%–50% for candidiasis and 70%–100% in the case of aspergillosis, with particularly poor outcomes in non-*Aspergillus* mold infections.[1–13]

Until a decade ago antifungal agents, such as amphotericin B, itraconazole and fluconazole, were mainly administered as conventional therapies for IFIs. However, amphotericin B is associated with dose-limiting toxicity and is only available as an intravenous (IV) formulation, itraconazole has been described with variable bioavailability and fluconazole has limited antifungal activity, mainly to yeasts and endemic fungi, eg, *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum*. Moreover, the emergence of resistance to these antimycotics is increasing amongst clinical isolates and shift in *Candida* spp. in candidiasis has been reported.[4] Therefore, new development of antimycotics with broad-spectrum activity was urgently needed. The second generation triazole voriconazole, besides the echinocandin caspofungin, is a new option for the management and monitoring of IFIs.[7–17]

Voriconazole is a synthetic derivative of fluconazole with the addition of a-methyl group and the replacement of a triazole ring with a fluorinated pyrimidine (Fig. 1) which increases the activity over the parent compound fluconazole.

Voriconazole, as an extended-spectrum triazole, is available in oral and IV formulations with a high bioavailability (96%) in adults, which makes its use easier in switch therapy from the intravenous to oral route. Population pharmacokinetic analyses of voriconazole in children 2 to 12 years of age have shown that an intravenous dosage of 7 mg/kg in young children yields a similar exposure of 3 to 4 mg/kg given to adults. Furthermore, oral bioavailability of

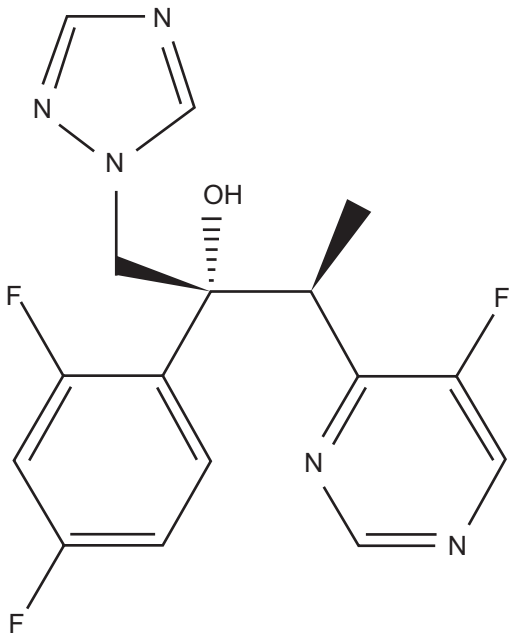

Figure 1. Voriconazole is designated chemically as (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol with an empirical formula of C16H14F3N5O.

voriconazole was found to be much lower (44.6%) in children than in adults (~96%).[20–22]

Additionally, voriconazole is cleared much more rapidly in children than in adults, and it exhibits distinctly different pharmacokinetic profiles in these two populations.[18–24] The oral formulation allows for reducing the duration of the hospital stay, given that it favours hospital discharge, and thus cost-effective therapy option.[18–23] Recent data suggest that topical application of voriconazole is also recommended in ocular infections. In fungal endophthalmitis, keratitis and skleritis it may be administered safely and effectively against a broad range of fungal pathogens.[18–30]

IV and oral voriconazole formulations are recommended in the USA in adults for the treatment of invasive aspergillosis, candidemia in non-neutropenic patients, disseminated infections caused by *Candida* spp., esophageal candidiasis and in patients with scedosporiosis and fusariosis who are refractory to or intolerant of other antifungal therapy[18,19] whereas in Europe IV and oral voriconazole formulations are recommended in both adults and pediatric patients of at least 2 years of age.[18,19,24]

It was approved by the FDA for clinical use in humans in 2002 for the treatment of invasive aspergillosis and as salvage therapy when patients fail standard

treatments for fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species, and in 2005 for the treatment of invasive candidiasis.[15,18–34] Recent guidelines suggest voriconazole as first-line therapy for treatment of invasive aspergillosis infection[15,31–33] and as an alternative treatment for patients with invasive *Candida* infections.[31–34]

Pharmacodynamic Properties

Mechanism of pharmacologic action

The mechanism of action of voriconazole is the same as for all other azole antifungals (itraconazole, fluconazole, ketoconazole), which is inhibition of cytochrome P-450-dependent 14α-lanosterol demethylation, thereby preventing the conversion of lanosterol to ergosterol. This is the critical step in fungal membrane ergosterol synthesis. This inhibition leads to accumulation of methylated sterol intermediates and depletion of ergosterol in fungal cells, which in turn disrupts the cell membrane and halts fungal growth.[13,34–39]

In vitro activity

Voriconazole has demonstrated activity both in vitro and in clinical infections against *Aspergillus fumigatus, A. flavus, A. niger*, and *A. terreus* species. *A. terreus* often expresses amphotericin B resistance. The majority of isolates studied in vivo and in vitro studies were *A. fumigatus* but several other *Aspergillus* isolates were noted in clinical trials. It also demonstrated variable in vitro activity against *Scedosporium apiospermum* and *Fusarium* species.

Voriconazole is fungistatic for most yeasts, but for *Aspergillus* species, it is fungicidal.[13,34–43] This increased activity against moulds may be attributable to increased activity at the site of action and a more complete inhibition of ergosterol synthesis.[13,39]

Voriconazole is active against the majority of *Candida* spp. including those resistant to fluconazole.[13] Against *C. guilliermondii, C. keyfr* and *C. lusitaniae*, voriconazole exhibited fungistatitic acitivity that was independent of drug concentration, but induced no post-antifungal effect at any concentration.[41] There is generally a 1–2 log reduction in minimum inhibitory concentrations (MICs) compared with fluconazole, although there have been isolates resistant to all azole antifungal substances. However, the safety and effectiveness of voriconazole in treating clinical infections due to *Candida lusitaniae* or *Candida guilliermondii* have not been established in adequate and well-controlled clinical trials. Voriconazole also demonstrates in vitro activity against other yeasts[1–13] including *Cryptococcus neoformans*, and dimorphic fungi *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum*.[42] Clinical data about efficacy for some of these mycoses are insufficient.

Obviously, therapeutic drug monitoring is well established when using medicines with narrow therapeutic indices to minimize toxicity.[43] Optimal therapeutic levels of voriconazole have not been described, but in phase II/III studies a median trough voriconazole level of 2.49 μg/mL was found. Although high voriconazole blood levels have been implicated in increased toxicity[27,37–44] and low levels to disease progression,[46] therapeutic and toxic levels of this agent are yet to be determined. Moreover, correlation between dose and levels is weak, and there is significant inter- and intrapatient voriconazole level variability.[47] According to Smith et al positive clinical response was observed in 100% of patients with random voriconazole concentrations of above 2.05 μg/mL, while disease progressed (and patients died) in patients with concentrations of below 2.05 μg/mL.[43] Neely et al found a pharmacodynamic association between voriconazole trough >1 μg/mL and survival and marked pharmacokinetic variability in children, particularly after enteral dosing, justifying the measurement of serum concentrations. Trough serum voriconazole concentration <1 μg/mL was associated with a 2.6-fold increased odds of death. Serum voriconazole concentrations were not associated with hepatotoxicity.[45] Tan and colleagues found that the absolute risk of liver function test abnormality in voriconazole treated patients is low.[46] There was no statistically significant relationship between plasma voriconazole concentrations and ALT abnormalities, whereas statistically significant, but weak, associations were identified between plasma voriconazole concentrations and AST and bilirubin abnormalities.

Denning et al reported that plasma concentrations below 0.25 mg/l correlated with a higher rate of clinical failure of invasive aspergillosis.[47] Three of five patients with concentrations below 0.25 mg/l failed to respond to therapy, whereas only one of six patients

with plasma concentrations between 0.25 and 0.5 mg/l failed to respond. Pascual et al used trough levels rather than random samples and showed a correlation between efficacy and plasma concentration.[48] Lack of therapeutic response was more common among patients with voriconazole trough concentrations less than 1 mg/L.

However, the optimal dosage regimens of voriconazole, based on pharmacokinetic and pharmacodynamic end points, are still to be analysed and developed.

Pharmacokinetics (Absorption, Distribution, Metabolism, Excretion)

Voriconazole is poorly soluble, despite structural similarity to fluconazole. Following oral administration, as either tablet or solution, bioavailability is 96%. Oral absorption is reduced by 22% when taken with food. Solubility of the intravenous formulation is achieved by sulfobutyl ether β-cyclodextrin (SBECD), a molecule pharmacologically similar to hydroxypropyl β-cyclodextrin. The oral solution does not contain SBECD. Voriconazole is 56% bound to serum proteins and independent of dose or plasma concentrations. The volume of distribution of voriconazole is 2–4.6 L/kg, suggesting extensive distribution into extracellular and intracellular compartments. And the drug is metabolized in the liver, mainly by CYP2C19 and CYP3A4 and to a lesser extent by CYP2C9 (Table 1).[35] Recently, the clearance of voriconazole via flavin-containing monooxygenase (FMO) was reported.[69] Steady-state concentration without a loading dose is achieved within 5 to 6 days of treatment. Voriconazole penetrates the blood-brain barrier, and CSF level is approx. 46% of the serum level. The percentages of voriconazole level in non-inflamed vitreous and aqueous humor are 38.1% and 53.0%, respectively.[26] The major metabolic pathways in humans involve fluoropyrimidine N-oxidation, fluoropyrimidine hydroxylation, and methyl hydroxylation. The main metabolite in serum is the inactive N-oxide.[49] Only 2% of the active drug is excreted in the urine. Voriconazole exhibits nonlinear pharmacokinetics due to saturation of metabolism, and small increases in dose result in exponential increases in blood levels. Voriconazole pharmacokinetics are also affected by, at least, CYP2C19 enzyme genetic variability.[50] Nineteen percent of the Asian and 2% of the Caucasian population are poor metabolizers in terms of CYP2C19 activity.[51,52] (homozygous for the CYP2C19 allele) resulting in high voriconazole blood levels. Higher percentages of patients are heterozygous for the CYP2C19 allele, leading to an intermediate metabolizer phenotype with moderately increased voriconazole blood levels. Patients with mild to moderate hepatic disease should get 50% of the usual maintenance dose. The safety of voriconazole has not been sufficiently established for liver cirrhosis and may not be used in this setting.[53,54] Due to accumulation of the intravenous voriconazole vehicle SBECD, the drug should be used with caution in patients with creatinine clearance of <50 mL/min.[55–57]

Table 1. Metabolism of voriconazole.

Enzyme system	Voriconazole
Inhibitor	
○ 2C9	++
○ 2C19	+++
○ 3A4	++
Substrate	
○ 2C9	+
○ 2C19	+++
○ 3A4	+

Note: + indicate the severity of inhibition or induction.

Pharmacokinetics in Special Populations

Gender

According to Purkins et al and Brüggemann et al gender influences the C_{max} concentrations and AUCτ of voriconazole. After multiple oral administration of voriconazole to healthy volunteers, young women (aged 18–45 years) had a 83% higher C_{max} and 113% higher AUC compared with young men. No significant differences in the mean C_{max} and AUC were observed between healthy elderly males and healthy elderly females (>65 years). In a similar study, after dosing with the oral suspension, the mean AUC for healthy young females was 45% higher than in healthy young males whereas the mean C_{max} was comparable between genders. The steady state trough voriconazole concentrations (C_{min}) seen in females were 100% and 91% higher than in males receiving the tablet and the oral suspension, respectively.[55–58]

In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female subjects were similar. Therefore, no dosage adjustment based on gender is necessary.[57–63]

Geriatric

In an oral multiple dose study the mean C_{max} and AUC in healthy elderly males (>64 years) were higher, respectively, than in young males (18–45 years). No significant differences in the mean C_{max} and AUC were observed between healthy elderly females (>64 years) and healthy young females (18–45 years). In the clinical program, no dosage adjustment was made on the basis of age. An analysis of pharmacokinetic from voriconazole clinical trials showed that the median voriconazole plasma concentrations in the elderly patients (>65 years) were higher than those in the younger patients (<64 years) after either IV or oral administration. However, the safety profile of voriconazole in young and elderly subjects was similar and, therefore, no dosage adjustment is necessary for the elderly.[61–64]

Pediatric

Initial pharmacokinetic studies in children demonstrated that the standard adult dosage of 4 mg/kg every 12 hours of intravenous (i.v.) voriconazole resulted in approximately 3-fold-lower plasma exposures in pediatric patients than in adults. Thus, a subsequent pharmacokinetic study of higher dosages was critically needed in order to understand the dosage of voriconazole (i.v.) in pediatric patients that would approach the median adult plasma exposure associated with the 4-mg/kg dosage that was effective in treatment of invasive aspergillosis. A population pharmacokinetic analysis was conducted on pooled data from 35 immunocompromised pediatric patients aged 2–11 years old who were included in two pharmacokinetic studies of intravenous voriconazole (single and multiple doses). Twenty four of these patients received multiple intravenous maintenance doses of 3 mg/kg and 4 mg/kg. A comparison of the pediatric and adult population pharmacokinetic data revealed that the predicted average steady state plasma concentrations were similar at the maintenance dose of 4 mg/kg every 12 hours in children and 3 mg/kg every 12 hours in adults.[63–71]

According to Walsh and colleagues the plasma pharmacokinetics of higher dosages of voriconazole needed to treat an immunocompromised pediatric patient population with exposures comparable to those of adult patients. In order to attain exposure of voriconazole in plasma comparable to that achieved with the 4 mg/kg i.v. dosage in adults, children aged <12 years old would need a dosage approaching 8 mg/kg. Oral bioavailability of voriconazole in children is much lower (44.6%) than that in adults (~96%), as mentioned above, suggesting the need for higher weight-adjusted oral dosages than those used for i.v. treatment.[20,24,68] However, due to very high interpatient variability and the nonlinear pharmacokinetic profile of voriconazole, formal dosing recommendations cannot be based solely on noncompartmental analysis. Nevertheless, when combined with an overall favorable safety profile indicating the absence of dose-dependent toxicity and the current exposure profiles, the current data reported here indicate that a dosage of voriconazole of approximately 8 mg/kg i.v. provides comparable and safe exposure in immunocompromised pediatric patients, Moreover, clearance of voriconazole in pediatrics is different. Voriconazole is eliminiated in children in a linear manner over the dosage range of 3 mg/kg every 12 hours (i.v.) and 4 mg/kg q12 hours (i.v.). And the capacity for elimination was higher compared with that in adults; this was possibly due to the greater systemic metabolism and greater firstpass metabolism with higher hepatic blood flow in children compared to adults.[20,68] Although oral dosing is unclear in general, according to European recommendations, a fixed 200-mg oral dose should be given twice daily in children aged 2–12 years, irrespective of age or weight. As a consequence, children with a low weight would receive a higher dose on a mg/kg basis than would those with a high weight. This is bewildering given that voriconazole dosing on the basis of body weight is recommended for the intravenous route, because previous results showed that weight significantly influenced the pharmacokinetics of intravenous voriconazole in pediatric population. Karlsson and colleagues reported that 7 mg/kg twice a day (BID) i.v. or 200 mg BID p.o., irrespective of body weight, was recommended for children. Loading doses or individual dosage adjustments according to

baseline covariates are not considered necessary in administering voriconazole to children.[20,22]

Adverse Events

The most frequently reported adverse events in the therapeutic trials were visual disturbances, fever, rash, vomiting, nausea, diarrhea, headache, sepsis, peripheral edema, abdominal pain, and respiratory disorder. The treatment-related adverse events which most often led to discontinuation of voriconazole therapy were elevated liver function tests, rash, and visual disturbances.[70–73]

Voriconazole is usually well tolerated; the most common adverse events after voriconazole treatment are visual changes, with an incidence of 20 to 23%.[71–73] Occurrence of 44.8% has been reported in one study.[74] Typically, the patients report blurred vision, photopsias, photophobia, and color changes 30 minutes to 1 hour after dosing. The symptoms are transient and reversible, almost never lead to drug discontinuation, and tend to dissipate after repeated dosing. The mechanism of action of the visual disturbance is unknown, although the site of action is most likely to be within the retina. In a study in healthy subjects investigating the effect of 28-day treatment with voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude, a decrease in the visual field, and an alteration in color perception. The ERG measures electrical currents in the retina.

As with all azoles, voriconazole can cause hepatotoxicity, mainly manifested by elevation of AST/ALT, which, on rare occasion, can be serious or lethal.[75] Both visual changes and hepatotoxicity have been associated with high voriconazole blood levels.[27] Visual and, rarely, auditory hallucinations can occur in less than 5% of patients[73] and should be distinguished from visual changes. Hallucinations are most often reported with the intravenous formulation and tend to disappear with the oral drug or with continued treatment. Confusion is less common. Skin rashes and cheilitis can occur after prolonged treatment, mainly due to photosensitivity. The mechanism underlying these dermatologic adverse events remains unknown.[76,77]

Although most commonly the rash is restricted to facial erythema in sun-exposed areas, more serious eruptions can occur necessitating discontinuation of the drug.[78] Pseudoporphyria, toxic epidermal necrolysis, and multifocal facial squamous cell carcinomas have also been reported.[79–81] Use of sunscreen should be advised, and appropriate guidance for sun exposure avoidance should be given in chronically treated patients. QT-prolongation and torsades de pointes should be considered in patients with predisposing factors.[82] Acutely painful extremities and peripheral neuropathy have been also described.[83] Voriconazole is teratogenic in animals and should not be used during pregnancy and is also not recommended during breast-feeding.[63,84]

Drug Interactions

Antifungal drugs have a high potential for drug–drug interactions, especially azoles, which exhibit a wide range and variety of drug–drug interactions. This is an ongoing concern in the treatment of IFIs. Drug interactions can be categorized as pharmacokinetic or pharmacodynamic.[58,85] Pharmacokinetic interactions occur at the level of drug absorption, distribution, metabolism or excretion. Frequently, the CYP450 metabolizing enzyme system and drug transporters, such as P-glycoprotein, are involved in these interactions In vitro studies with human hepatic microsomes show that voriconazole inhibits the metabolic activity of the cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. In these studies, the inhibition potency of voriconazole for CYP3A4 metabolic activity was significantly less than that of two other azoles, ketoconazole and itraconazole, but more potent CYP3A4 inhibition than fluconazole or posaconazole. In vitro studies also show that the major metabolite of voriconazole, voriconazole N-oxide, inhibits the metabolic activity of CYP2C9 and CYP3A4 to a greater extent than that of CYP2C19. Therefore, there is potential for voriconazole and its major metabolite to increase the systemic exposure (plasma concentrations) of other drugs metabolized by these CYP450 enzymes.[58,85,87–102] Triazoles have numerous clinically significant drug interactions, the list is constantly expanding and the majority of those currently identified are presented in Table 2[17,85,86,91–102] and Table 3.[52–55,57,62,75–82,86] Most of these interactions arise from competitive inhibition of liver oxidative metabolism via rapid reversible binding to

Table 2. Effect of voriconazole on pharmacokinetics of co-administered drugs.

Drug (mechanism of interaction by voriconazole)	Drug plasma exposure (C_{max} and AUC)	Recommendations for voriconazole dosage adjustment/comments
Alfentanil (CYP3A4 inhibition)[86]	Significantly increased	Reduction in the dose of alfentanil and other opiates metabolized by CYP3A4 (eg, sufentanil) should be considered when co-administered with voriconazole
Alprazolam[a]; benzodiazepines (CYP3A4 inhibition)[91]	Potential for voriconazole to inhibit metabolism (increased plasma exposure)	Frequent monitoring for adverse events and toxicity (ie, prolonged sedation) related to benzodiazepines metabolized by CYP3A4 (eg, midazolam, triazolam, alprazolam)
Astemizole, Cisapride, Terfenadine, Pimozide, Quinidine (CYP3A4 inhibition)[85,96]	Not studied in vivo or in vitro, but drug plasma exposure likely to be increased	CI because of potential for QT prolongation and rare occurrence of torsade de pointes
Carbamazepine (CYP2C9 inhibition)[85]	Significantly increased	CI carbamazepine may reduce the C_{max} voriconazole
Cyclosporine (CYP3A4 inhibition)[87]	AUC significantly increased; no significant effect on C_{max}	
Digoxin (P-glyco protein-induced transport)[32]	No significant change	
Ergot alkaloids (CYP3A4 inhibition)[88]	Not studied, but drug plasma exposure likely to be increased	CI (neurotoxicity due to "ergotism")
Felodipine (dihydropyridine calcium channel blockers (CYP3A4 inhibition)[b,85]	Potential for voriconazole to inhibit metabolism (increased plasma exposure)	Frequent monitoring for adverse events and toxicity related to calcium channel blockers
Glimepiride (CYP2C9 inhibition)[97]	Increased	Hypoglycemia
Ibuprofen, NSAIDs (CYP2C9 inhibition)[89]	Increased	Frequent monitoring for adverse events and toxicity related to NSAIDs
Lovastatin; Statins (CYP3A4 inhibition)[d,96]	In vitro studies demonstrated potential for voriconazole to inhibit metabolism (increased plasma exposure)	Frequent monitoring for adverse events and toxicity related to statins (rhabdomyolysis)
Methadone (CYP3A4 inhibition)[90]	Increased	Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation; dose reduction of methadone may be needed
Methylprednisolone (CYP3A4 inhibition)[e,94]	Increased	
Omeprazole (CYP2C19-inhibition; CYP2C19- and CYP3A4-substrate)[92]	Increased	No voriconazole dosage adjustment is necessary
Phenytoin (CYP2C9 inhibition)[93]	Significantly increased	frequent monitoring of phenytoin plasma concentrations and frequent monitoring of adverse effects related to phenytoin
Rifabutin (CYP3A4 inhibition)[95]	Significantly increased	CI
Ritonavir (CYP3A4 inhibition)[104]	No significant effect of voriconazole on ritonavir C_{max} or AUC	CI because of significant reduction of voriconazole C_{max} and AUC
Sirolimus (CYP3A4 inhibition)[85,98]	Significantly increased	CI
Tacrolimus (CYP3A4 inhibition)[99,100]	Significantly increased	Reduce the tacrolimus dose to one-third of the starting dose and follow with frequent monitoring of tacrolimus blood levels (nephrotoxicity)
Warfarin (CYP2C9 inhibition)[101]	Prothrombin time significantly icreased	Monitor PT or other suitable anticoagulation tests; adjustment of warfarin dosage
Zolpidem (CYP3A4 inhibition)[102]	Significantly increased	

Notes: [a]Includes most benzodiazepines except: bromazepam, diazepam, temazepam, and estazolam; [b]Includes most calcium channel inhibitors; [c]Includes glyburide and tolbutamide; [d]Includes simvastatin and atorvastatin but not pravastatin, fluvastatin, and rosuvastatin; [e]Includes betamethasone, dexamethasone, hydrocortisone, fludrocortisone, budesonide, and fluticasone, but not prednisolone.
Abbreviation: CI, contraindication.

Table 3. Effect of co-administered drugs on voriconazole pharmacokinetics.

Drug (mechanism of interaction)	Voriconazole plasma concentration (C_{max} and AUC)	Recommendations for voriconazole dosage adjustment/comments
Rifampin, rifabutin (CYP450 induction)[95]	Significantly reduced	CI
Ritonavir (CYP450 induction)[104]	Significantly reduced/reduced	CI
Carbamazepine (CYP450 induction)	Not studied in vivo or in vitro, but likely to result in significant reduction	CI
Long acting barbiturates (CYP450 induction)[85]	Studied in vivo or in vitro, but likely to result in significant reduction	CI
Phenytoin (CYP450 induction)[85,93]	Significantly reduced	Increase voriconazole maintenance dose
St. John's Wort (CYP450 inducer)[103]	Significantly reduced	CI
Oral contraceptives containing ethinyl estradiol and norethindrone (CYP2C19 inhibition)[57]	Increased	Monitoring for adverse events and toxicity related to voriconazole
HIV protease inhibitors (CYP3A4 inhibition)[104–107]	In vivo studies showed no significant effects of indinavir on voriconazole exposure	No dosage adjustment
	In vitro studies demonstrated potential for inhibition of voriconazole metabolism (increased plasma exposure)	Frequent monitoring for adverse events and toxicity related to voriconazole
NNRTIs (CYP3A4 inhibition or CYP450 induction)[105–110]	In vitro studies demonstrated potential for inhibition of voriconazole metabolism by delavirdine and other NNRTIs (increased plasma exposure)	Frequent monitoring for adverse events and toxicity related to voriconazole
	Voriconazole-Efavirenz Drug Interaction study demonstrated the potential for the metabolism of voriconazole to be induced by efavirenz and other NNRTIs (decreased plasma exposure)	Careful assessment of voriconazole effectiveness

Abbreviations: CI, contraindicated; NNRTIs, Non-Nucleoside Reverse Transcriptase Inhibitors.

CYP450 system enzymes (phase I metabolism). Voriconazole interferes mainly with CYP3A4, CYP2C9, and CYP2C19 with distinctive affinity and, accordingly, it exhibits slightly different drug interaction profiles compared to other azoles.[13,35,113] Among the most significant common drug interactions of triazoles are drug elevations of cyclosporine, tacrolimus, and sirolimus, most calcium channel blockers, most benzodiazepines, many statins and steroids, warfarin, and rifabutin (Table 2). Although not studied in vitro or in vivo, carbamazepine and long-acting barbiturates (eg, phenobarbital, mephobarbital) are likely to significantly decrease plasma voriconazole concentrations. Coadministration of voriconazole with carbamazepine or long-acting barbiturates is contraindicated. Carbamazepine, phenytoin, rifampin, and rifabutin significantly decrease azole concentrations (Table 3). Increased blood levels of terfenadine, astemizole, cisapride, pimozide, and quinine can cause QT prolongation and predispose to torsades de pointes. Increased cytotoxic chemotherapy-related toxicity can be caused by concomitant treatment with voriconazole and vinca alkaloids, cyclophosphamide, vinorelbine, and busulfan.[85–112] Therefore, careful monitoring and/or dosage adjustment of these drugs is needed.

Voriconazole's pharmacokinetic profile is not influenced by antacids or proton pump inhibitors.[86,93] The mean maximum plasma concentrations (C_{max}) and area under the curve (AUC) of voriconazole were clinically irrelevantly increased by 15% by omeprazole due to the inhibition of plasma clearance of voriconazole.[93] Single and multiple oral administration of voriconazole with food lowered the bioavailability by approximately 22% and delayed absorption compared with a fasting state. Administration of voriconazole

with a high-fat meal reduced mean C_{max} and AUC by 34% and 24%, respectively. For this reason, oral dose administration is recommended either 1 hour before or 1 hour after meals.[63,95]

Resistance

There are several mechanisms of fungal resistance to azole antimycotics. These include overexpression of the target enzyme, point mutations in fungal enzymes, or the appearance of efflux pumps.[118] Voriconazole resistance development has not been adequately studied in vitro against *Candida, Aspergillus, Scedosporium* and *Fusarium* species. The frequency of drug resistance development for the various fungi for which this drug is indicated is not well known.[63,114–119]

In contrast to voriconazole, fluconazole has limited antifungal activity, mainly to yeasts and endemic fungi, eg, *Coccidioides immitis, Blastomyces dermatitidis,* and *Histoplasma capsulatum*. In the last few years, resistance of *A. fumigatus* to itraconazole has been found to be due to different mechanisms including reduced intracellular accumulation, overexpression of the target enzyme and the presence of point mutations in the *cyp51A* gene which codes for the target enzyme 14-α-sterol demethylase.[120,121] The number of reports of resistance of clinical isolates of *A. fumigatus* to voriconazole and multi-azole resistance is gradually increasing.[122–124] The development of resistance in an *Aspergillus fumigatus* isolate, originally sensitive to itraconazole and voriconazole, recovered from a case of pulmonary aspergilloma treated with voriconazole was described by sequencing of the gene with described the G448S mutation in *cyp51A* gene after prolonged treatment with voriconazole.[126]

Voriconazole in Clinical Trials

Opportunistic fungal infections are a major cause of morbidity and mortality in neutropenic cancer patients and antifungal therapy are used both empirically and therapeutically in these patients. Few clinical trials compared the benefits and adverse effects of voriconazole with those of amphotericin B and fluconazole when used for prevention or treatment of invasive fungal infections in cancer patients with neutropenia. The antifungal agent was given empirically in one trial[73] and as treatment in one trial.[74]

Walsh et al mainly included patients with leukemia, but also other types of cancer, and patients who had undergone transplantation with hematopoietic stem cells. Herbrecht et al[74] included patients with definite (39%) or probable (61%) invasive *Aspergillus* infection with a similar distribution of underlying disease as in Walsh et al trial.[73]

In Walsh's randomized comparison of voriconazole with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever, the activity of voriconazole in the prevention of breakthrough fungal infections is consistent with its efficacy in a recently completed clinical trial involving primary treatment of documented invasive aspergillosis.[126] These effects may be related to the combination of its potent in vitro antifungal activity and its pharmacokinetic properties.[1–23,74] An advantage is also the low molecular weight of voriconazole which may permit penetration into the endobronchial-lining fluid and other mucosal surfaces.[73] Empirical antifungal therapy with voriconazole should be used in patients with persistent neutropenia, who are at high risk for invasive antifungal infections. In the prospectively defined high-risk group in our study, the overall response rate among patients who received voriconazole was similar to the rate among those who received liposomal amphotericin B, and the frequency of breakthrough fungal infections was significantly reduced in the voriconazole group.[73]

Wingard and his colleagues also report that voriconazole as first-line for treatment of invasive aspergillosis resulted in significantly fewer deaths as compared to those treated with conventional amphotericin B. Hospital-free survival was significantly greater for patients initially treated with voriconazole, thus this antimycotic has shown to be cost-effective.[127]

In another randomized unblinded trial by Herbrecht and colleagues patients with invasive aspergillosis who were initial therapy with voriconazole showed better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B,[74] although liposomal amphotericin B is well known to have significantly lower infusion-related toxicity than conventional amphotericin B, severe acute reactions have been described.[73] By comparison, the only significant infusion-related reaction to voriconazole

was transient photopsia, which was not associated with discontinuation of therapy. In brief, the study by Herbrecht and colleagues shows the superiority of voriconazole over amphotericin B as initial therapy for invasive aspergillosis, in terms of response rate, survival rate, and safety.

Summary

Voriconazole is a promising triazole compound derived from fluconazole with enhanced activity against a variety of fungal species. Voriconazole is available as an oral and intravenous product, and may become the drug of choice for *Scedosporium* and *Fusarium* infections; however, because of adverse events, drug interactions, and evolving efficacy literature, it should not supplant fluconazole as first-line therapy for most candidal infections. The data for the use of voriconazole as a first-line agent in aspergillosis are strong and favor use over all amphotericin B formulations. The oral formulation offers a potent, consistently bioavailable product for the management of aspergillosis for patients with a functional gastrointestinal tract. The clinician must consider the multiple, potential drug interactions and adverse events when considering voriconazole. Despite these limitations, voriconazole offers a significant advance in azole antifungals and a welcomed addition to the antifungal armamentarium. However, resistance to voriconazole has been reported in *Aspergillus* species.

Disclosure

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