VORICONAZOLE – BETTER CHANCES FOR PATIENTS WITH INVASIVE MYCOSES

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Abstract: The past two decades have witnessed an increase in serious fungal infections, without corresponding growth in available antifungal agents. Voriconazole (VRC) is a novel triazole antifungal, recently approved in Europe for treatment of serious infections caused by Aspergillus, Fusarium, Scedosporium, and resistant Candida species. Voriconazole has in vitro activity against yeasts and yeast-like fungi; similar, or superior to, fluconazole (FLC), itraconazole (ITC) and amphotericin B (AMB). Candida albicans is generally the most susceptible yeast (VRC MIC90 of 0.06 µg/ml); C. krusei often has low MICs even in the face of FLU/ITC resistance. Voriconazole has demonstrated comparable, or better, in vitro activity than ITC and AMB against Aspergillus (mean MICs 0.19-0.58 µg/ml), Aspergillus, Bipolaris, Fusarium, Blastomyces dermatitidis, Coccioidoides immitis, dermatophytes, Histoplasma capsulatum, Malassezia, and Scedosporium angleseum (P. boydii). The drug possesses potent fungicidal activity against moulds including Aspergillus, Scedosporium, and Fusarium. Fungicidal activity is likely due to the high affinity of VRC for fungal 14-α-demethylase, a concept supported by ultrastructural and biochemical analysis. Animal studies confirmed the activity of VRC against infections including Aspergillus infections (IA); A. fumigatus endocarditis; fusariosis; pulmonary cryptococcosis; and invasive candidiasis. Most importantly, well-designed human clinical trials have confirmed the efficacy of VRC in the treatment of candidal esophagitis, IA, and febrile neutropenia. Smaller studies and case reports have shown VRC is useful for salvage therapy of IA, cerebral aspergillosis, Scedosporium, and other fungal infections. Clinical testing has shown VRC is safe and well tolerated; the most common side effect is benign, self-limited visual disturbance.

Key words: Voriconazole; Candida; Aspergillus; Scedosporium; Fusarium; azole; triazole; mycoses; treatment

1. INTRODUCTION

Recent years have witnessed a significant increase in the incidence of fungal infections, including those caused by yeast and filamentous fungi. In the United States Candida species are now the fourth most common nosocomial blood stream pathogen (8%) with the highest crude mortality (40%) [25]. In Europe, Candida spp. are the eighth most common cause (2.8%) of blood-stream infections (whether nosocomial or community-acquired). In a review of 11,000 autopsies conducted at a University Hospital in Europe, Groll et al. [48] documented an increase in invasive mycoses, largely due to a rise in Aspergillus infections (P < 0.001). The incidence of invasive aspergillosis (IA) among transplant patients increased from 6% to 11% between 1983 and 1992. A similar increase in the incidence of organisms other than Aspergillus has been reported by Singh et al., who showed that fungi other than Aspergillus accounted for 37% of all moulds [93]. Unfortunately, the increase in the incidence of fungal infections is associated with a dramatic increase in mortality. McNeil et al. [70] reported a 3.4-fold increase in mortality due to fungal infections from 1980 to 1997. These authors showed that fungal infections climbed from the 10th to 7th position in a ranking of infectious causes of death in the US, during the same time period.

The increase in the incidence of fungal infections and associated mortality, and the emergence of resistance to currently used antifungal agents [for reviews see references 42 and 106] intensified the search for new, safe and broad-spectrum agents. These efforts led to the introduction of terbinafine (belonging to the allylamine class of compounds) for the treatment of dermatophytosis, and amphotericin B (AmB) lipid formulations (e.g. Abelcet and AmBisome) with improved safety profiles compared to standard AmB [40, 59]. Additionally, members of a new class of antifungal agents, the echinocandins (which target fungal cell walls), are being developed. Caspofungin has been approved by the FDA (for the treatment of IA in patients refractory to, or intolerant of, other therapies); micofungin (Fujisawa) and anidulafungin (Versicor) are undergoing phase II/III clinical trials.

However, with 15 different drugs marketed worldwide, and at least three new investigational drugs under development [voriconazole (Vfend™;
Pfizer), posaconazole (Schering-Plough), and ravuconazole (Bristol-Myers-Squibb), the azoles are currently the most widely used and studied class of antifungal agents for topical and systemic mycoses [55]. This review will provide an overview of the properties of voriconazole (VRC), a highly promising new, second-generation triazole. We are focusing on this agent since it has recently been approved by the EU for the treatment of invasive aspergillosis, Scedosporium, and Fusarium infections, as well as fluconazole-resistant serious Candida infections, and due to our extensive involvement in its in vitro and in vivo evaluation [8, 28, 41, 61, 90]. The information contained in this review has been obtained from over 100 peer-reviewed articles, abstracts presented at national meetings, and Pfizer internal data (supplied to investigators).

2. HISTORICAL PERSPECTIVE

Although the firstazole antifungal agent was reported in 1944 [29], it was not until 1958 that topical chormidazole became available for clinical use [92]. Two more topical azole antifungal agents, miconazole and clotrimazole, were introduced in 1969, followed by econazole in 1974 [92], and a parenteral formulation of miconazole in the late 1970s [10, 46]. Today, these three agents remain the mainstay of topical therapy for many superficial mycoses such as tinea pedis and candidal vaginitis.

By 1980, the only new azole introduced for the treatment of systemic fungal infections was oral ketoconazole (KTC) [59]. It would be more than 10 years before either fluconazole (FLC) or itraconazole (ITC) became available for the treatment of systemic mycoses [7]. Itraconazole, first licensed in 1992, was initially available only in a capsule form that was plagued by poor and erratic bioavailability [49]. However, in 1997 the FDA approved an oral solution formulated with a vehicle that facilitated absorption, and in 1999, an intravenous form with the same vehicle was approved. The introduction of FLC and ITC improved our ability to manage fungal infections, particularly candidiasis. However, these first generation triazoles suffer from a narrow spectrum of activity (FLC has a poor activity against some yeasts and moulds), and the emergence of resistance. To circumvent these shortcomings, an extensive research program was undertaken by Pfizer Pharmaceuticals that led to the discovery of VRC, a novel, broad-spectrum antifungal agent which demonstrated activity against azole-resistant species of Candida, including Candida krusei and C. glabrata, as well as activity against moulds such as Aspergillus [54].

3. CHEMISTRY

Voriconazole has close structural similarity to FLC (Fig. 1), with a molecular formula of C17H11N3O3F2, corresponding to a molecular weight of 349.3. It is a white powder that is soluble (at room temperature) in 0.1 M HCl (2.96 mg/ml), with a melting point of 128-134 °C. For in vitro experimental purposes, stock solutions of 1 mg/ml can be made up in dimethyl sulfoxide (DMSO). The IV preparation of VRC is prepared with sulphobutyl ether β-cyclodextrin (SBECD), a novel solubilizing agent.

4. ANTIFUNGAL ACTIVITY

i) IN VITRO

Extensive in vitro susceptibility testing of VRC (more than 600 fungal isolates were tested, including yeasts, yeast-like organisms, and moulds) clearly demonstrated the broad-spectrum activity of this drug. In general, VRC had in vitro activity against most yeasts and yeast-like fungi [minimum inhibitory concentration (MIC) of <2 μg/ml] that was similar or superior to that of FLC, ITC and AmB [6, 8, 12, 13, 15, 60, 75, 76, 84, 89, 90]. Candida albicans is generally the most susceptible yeast, with a VRC MIC50 (the concentration of drug causing a 90% growth inhibition of organisms) of 0.06 μg/ml, while C. glabrata is the least sensitive with an MIC50 of 2.0 μg/ml [83].

Voriconazole has demonstrated comparable, or better, in vitro activity than ITC and AmB against filamentous and dimorphic fungi including Aspergillus spp., Ascomycetes, Bipolaris spp., Fusarium spp., Blastomyces dermatitidis, Coccidioides immitis, dermatophytes, Histoplasma capsulatum, Malassezia spp., Scedosporium angiospermum (P. boydii), Rhizopus arrhizus, Sporothrix schenckii, and Absidia corymbifera [16, 17, 26, 45, 68, 69, 77, 86, 107, 108] although activity against the latter three species was much less than against other organisms [58, 65].

Due to the increased incidence (and high attributable mortality) of filamentous fungal infections, potent activity against moulds is an important parameter for any new antifungal agent. Studies with VRC have demonstrated its high activity against Aspergillus species in vitro (mean MICs 0.19–0.58 μg/ml). Importantly, published reports revealed that VRC possesses a potent fungicidal activity (at tissue concentrations approximately twice the MIC) against moulds including Aspergillus spp, Scedosporium (Pseudallescheria) spp. and Fusarium spp. [minimum fungicidal concentration (MFC) of 0.71–0.36 μg/ml] [5, 6, 16, 53, 73, 89]. It has been postulated that structural changes introduced in VRC result in a higher affinity (compared to other azoles) for the fungal 14α-demethylase, leading to cell death (Dr. C.A. Hitchcock, personal communication). There does not appear to be cross-resistance with AmB, likely due to the different sites of action of the two agents [1], and in fact one study found VRC to be effective in vitro against AmB-resistant Aspergillus terreus [94]. The finding of fungicidal activity against moulds may have important clinical implications, since to date azoles have been considered
fungistatic agents. This has been at least a theoretical limitation to azole therapy, since traditionally static agents have been felt inferior to cidal agents in many serious bacterial and fungal infections.

The antifungal activity of VRC against a small number of Zygomycetes spp. was evaluated in vitro, and compared to that of AmB and ITC. Of the three agents, only AmB had good antifungal activity: MICs ranged from 2 to $\geq 32$ $\mu$g/ml and from 0.06 to 8 $\mu$g/ml for VRC and AmB, respectively. However, the activity of ITC appeared more species-dependent, with some organisms being susceptible (MICs from 0.25 to 2 $\mu$g/ml), while others resistant (MICs $\geq 32$ $\mu$g/ml). Overall, it may be assumed that VRC has poor activity against zygomycetes. An extensive summary of VRC MIC testing for various organisms was recently published [27].

ii) IN VIVO

Voriconazole is eliminated much less rapidly in guinea pigs, than in other small laboratory mammals (e.g. mice, rats, and rabbits), which tend to exhibit auto-induction of metabolism. The prolonged systemic VRC levels in guinea pigs are comparable to those observed in humans [57]. As such, the guinea pig was selected as the most appropriate animal model for evaluation of the in vivo efficacy of VRC. Using this model, the efficacy of VRC has been demonstrated against a wide variety of fungal infections including invasive and pulmonary aspergillosis [30]; A. fumigatus endocarditis [67]; pulmonary cryptococcosis [97]; and invasive candidiasis caused by C. albicans, C. glabrata, and C. krusei [78, 88, 97].

Taken together, data from these studies showed VRC could be an effective treatment for aspergillosis in both immuno-competent and immuno-compromised animal models, and thus by extension, human patients. Moreover, it appeared efficacious for the treatment of infections caused by FLC-susceptible and -resistant Candida species. Finally, animal models suggested VRC was superior to AmB in cryptococcosis [for a detailed description of these studies please see reference 54].

5. MECHANISM OF ACTION

Azole antifungals are divided into two groups on the basis of structure: the imidazoles ( clotrimazole, miconazole, KTC), which have a five-membered ring with two nitrogens; and the triazoles (FLC, ITC, VRC, posaconazole, ravuconazole),
which have a five-membered ring with three nitrogen(s) (Fig. 1). These drugs exert their effects primarily by inhibiting the fungal cytochrome P450 CYP3A enzyme lanosterol 14-α-demethylase, preventing the conversion of lanosterol to ergosterol. (The main azole target is likely the heme protein which co-catalyzes the 14-α-demethylation of lanosterol [52]). This in turn leads to depletion of ergosterol (a regulator of fungal cell membrane fluidity and asymmetry) and accumulation of sterol precursors, including the 14-α-methylated sterols lanosterol, 4,14-dimethylzymosterol, and 24-methylenedihydrolanosterol. As a result of ergosterol depletion, the integrity and function of the fungal cell membrane is disrupted, eventually leading to cell lysis [39]. Figure 2 is a summary of the ergosterol biosynthetic pathway showing sites of action of antifungal agents, including VRC.

At a genetic level, data supporting this mechanism of action comes from several elegant studies by Geber et al. [32]. These authors cloned the 14-α-methyl sterol demethylase (ERG11) and Δ^{24}-sterol desaturase (ERG3) genes from C. glabrata, and in turn used them to create deletion mutants lacking one or both genes. Phenotypic analysis revealed that the ERG3 deletion mutant remained susceptible to FLC and ITC. In contrast, the ERG11 and ERG11/ERG3 deletion mutants were resistant to FLC (100 µg/ml), ITC (16 µg/ml) and AmB (2 µg/ml).

At a biochemical level, our group investigated the influence of sub-inhibitory concentrations of VRC and FLC on sterol biosynthesis of FLC-resistant and -susceptible C. albicans and C. krusei [90]. Voriconazole-treated C. albicans strains showed profound changes in sterol profile, including complete inhibition of ergosterol synthesis and accumulation of its precursors [90]. In C. krusei, VRC treatment resulted in significant inhibition of ergosterol synthesis (>75% inhibition) and accumulation of methylated intermediates. In contrast, FLC treatment had a minimal effect on C. krusei sterols. These results support the premise that VRC is a superior inhibitor of fun-

Fig. 2. Summary of ergosterol biosynthetic pathway showing sites of action of antifungals.

Fig. 3. Transmission electron micrographs showing the effect of voriconazole treatment on the morphology of Candida glabrata. (A) Normal, untreated control; (B) Voriconazole-treated cells. Magnification x 13,500.
gal 14-α-demethylase, compared to traditional azoles.

Ultrastructural analyses (using scanning and transmission electron microscopy) have revealed that the depletion of ergosterol by VRC results in significant changes in the morphology of susceptible species. Voriconazole-treated C. krusei and C. glabrata isolates exhibited pronounced separation of the cell wall and cytoplasm, cell membrane degradation, and thinning of the cell wall [see Fig. 3 as well as reference 8]. Unlike control (Fig. 4A), voriconazole treatment also caused a cessation of cell division manifested by elongation (Fig. 4B) and enlargement of C. albicans blastospores (Fig. 4C). In contrast, FLC had no effect on the ultrastructure of the intrinsically FLC-resistant C. krusei. These microscopic images appear to clearly demonstrate the increased potency of VRC (over FLC) against C. krusei 14-α-demethylase.
While the azoles also block mammalian cholesterol synthesis at 14-α-demethylation, the dose required to cause the same degree of inhibition is much higher than that required for fungi [52, 100, 101]. For example, Hitchcock et al. [53] showed that VRC had an inhibitory concentration (IC₅₀) of 7.4 μM against the 14-α-sterol demethylase of rat liver, while the IC₅₀ against the fungal enzyme was as low as 0.03 μM. Thus VRC is about 250-fold more active against the fungal than the mammalian demethylase enzyme. VRC and FLC are less active than KTC and ITC against mammalian P-450-dependent steroid hormone biosynthesis, suggesting the former two agents are more selective inhibitors of fungal P-450 sterol biosynthesis. Indeed, clinical effects of inhibition of human sterol biosynthesis are most prominently seen with KTC.

6. RESISTANCE

A number of mechanisms of Candida resistance to azoles have been well described. These include alterations in the drugs' target (14-α-demethylase), modifications of sterol synthesis, reduction or over-expression of the target enzyme, and induction of drug efflux pumps [for review see references 42 and 106]. Similar molecular mechanisms underlying Aspergillus resistance to ITC have been found [23, 44, 62, 63, 79].

Since breakpoints have not been established for the investigational triazoles [VRC, ravuconazole, and posaconazole], detailed discussion of resistance is not possible. However, early data suggest that C. albicans isolates resistant to ITC, or FLC are also less susceptible to the new investigational triazoles [14, 18]. Moreover, FLC-resistant C. glabrata isolates are almost always resistant to ITC and less susceptible to the investigational azoles [82]. However, cross-resistance is not a for­gon conclusion, and the actual impact on clinical efficacy remains to be determined [62, 72, 98].

Interestingly, no cross-resistance is observed in the case of C. krusei; this species tends to have low MICs to VRC even in the face of resistance to FLC and ITC [82]. In an elegant analysis of cross-resistance among licensed and investigational triazoles, Pfäffer showed that to express high MICs to VRC, C. albicans and C. glabrata isolates had to be resistant to both FLC and ITC. Isolates that are resistant to FLC alone tend to have low VRC MICs (10% of the isolates inhibited at 0.5 μg/ml) [82].

Mechanisms underlying this phenomenon are unknown, but from Pfäffer's data it can be postulated that for an isolate to become resistant to VRC, more than one resistance mechanism must be induced simultaneously (e.g., alteration of 14-α-demethylase and over-expression of drug efflux pumps).

7. PHARMACOKINETIC CONSIDERATIONS

Voriconazole's pharmacokinetic profile has been characterized following oral and intravenous ad­ministration in different animal species including mice, rats, guinea pigs, rabbits, and dogs. However these will not be discussed in this article, and interested readers are referred to the following two references [54, 57]. Here we will instead focus on human data.

The pharmacokinetics of VRC have been investigated in more than 500 healthy volunteers following single and multiple-dose, oral (PO) and intravenous (IV) dosing [80]. These studies showed VRC is rapidly absorbed following oral administration, with a time to maximal concentra­tion (Tmax) of < 2 hours and a half-life (t1/2) of approximately 6 hours. Due to saturation of metabolicism, VRC exhibits non-linear pharmacokinetics. The bioavailability of oral VRC (up to 96%) is better than that of ITC [80]. Furthermore, the absorption is not affected by gastric pH, and hence antacids, as is the case with ITC capsules (although the newer ITC solution does not suffer from this problem). Subjects given VRC 350 mg twice daily had a Cmax (maximum concentration of drug in plasma) of 5.0 mg/L, Tmax of 3.0 h, and AUC (area under the concentration-time curve) of 40.5 mg·h/L on day 14 [9]. The volume of distribution was 4.6 L/kg, implying wide tissue distribution. The concentration of VRC in the saliva is approximately 65% of that in plasma, consistent with a plasma protein binding of 58% [2]. The t1/2 of about 6 hours after a single dose suggests that twice-daily dosing is required.

In vitro studies using human microsomes have shown that VRC is metabolized primarily by the hepatic cytochrome P450 iso-enzymes CYP2C19, CYP2C9 and CYP3A4, with CYP2C19 being the major metabolic iso-enzyme [95]. Elimination of VRC occurs primarily via metabolic clearance by the liver; less than 2% is excreted unchanged in the urine or feces. However, about 80% of the original dose is excreted in the urine, and 20% in the feces, implying that dosage adjustments may be necessary for either renal or hepatic failure [3]. One pharmacokinetic study in patients with chronic hepatic impairment confirmed that while such patients should receive the normal loading dose (400 mg orally every 12 hours on day 1), the maintenance dose should be cut in half (to 100 mg twice daily) [95]. Conversely, the equivalent pediatric IV maintenance dose should be 4 mg/kg, instead of 3 mg/kg (the adult IV maintenance dose), reflecting higher rates of clearance in children [102]. Eight metabolites of VRC have been characterized (3 major and 5 minor). Using a range of methodologies, none of the metabolites have been shown to exhibit appreciable antifungal activity.

Human studies showed that achievable plasma steady-state concentrations (>2 μg/ml) of VRC after PO and IV administration are well above its MICs for Candida spp. [0.001-0.39 μg/ml], Aspergillus (0.35-0.58 μg/ml), Cryptococcus neoformans (0.24 μg/ml) and most emerging mycoses [see above, and also reference 53]. However, these investigations also revealed that there was notable inter-subject variability in Cmax following both
oral and intravenous administration. Such variability in \( C_{\text{max}} \) after oral dosing implies differences in bioavailability and/or volume of distribution (Vd). Any variability in \( C_{\text{max}} \) after IV dosing is only due to differences in Vd. The finding of inter-subject variability in VRC AUC may be attributable to differences in the ability of individuals to metabolize CYP2C19 substrates (see below).

Tissue penetration may be an important determinant in clinical outcome. Whole body autoradiography was used to assess the distribution of radioactivity in the tissues of rats (both females and males) after a single IV administration of \([^{14}C]\)-VRC at a dose level of 15 mg/kg [57]. Radioactivity was rapidly and extensively distributed throughout tissues. Drug concentrations were highest in the liver and adrenal cortex. There were no differences between male and female animals. Tissue concentrations of radioactivity at 5 minutes post infusion were (in µg/g): 4.3 in blood, 8.1 in brain, 13 in eye (retina), 12.4 in kidney (cortex), 21.1 in liver, and 5.8 in lung. The high levels in brain and ocular tissue may have clinical implications, since traditionally these are very difficult areas to treat successfully. In fact, there are now several anecdotal case reports of successful therapy of Aspergillus, Scedosporium, and Fusarium infections at these sites [74, 87, 91]. The high concentrations in liver may also have significance in the treatment of hepatosplenic candidiasis [56].

The toxicity of the cycloextran vehicle has also been studied. In animal studies using repeated-dose IV SBECD, vacuolation of renal tubular epithelial cells in rats and dogs were seen, which is common in animals receiving substituted β-cycloextrans. However there was no degeneration, necrosis, or pseudocrystal formation in renal epithelial cells and no deterioration of renal function [3]. In human volunteers (single and multiple dose studies), there were no changes in urinary protein, N-acetylglucosaminidase, and β-2-microglobulin levels, which would have indicated effects on renal integrity or renal tubular small protein reabsorption. Overall the studies do not suggest a potential toxic effect to the kidney. It was also found that SBECD is well tolerated and rapidly cleared [96]. Ninety-five percent of the compound is renally excreted, and the majority cleared within 6 hrs.

8. Drug-Drug Interactions

As discussed above, VRC primarily inhibits the fungal cytochrome P450 CYP3A enzyme lanosterol 14-a-demethylase, preventing the conversion of lanosterol to ergosterol, and thus disrupting the integrity and function of the fungal cell membrane. However, the drug (like other azoles) is both a substrate and inhibitor of human CYP2C19, CYP2C9, and CYP3A4. While VRC has greater affinity (and hence inhibition potency) for the former 2 iso-enzymes, notably its inhibition potency against CYP3A4 (likely the most clinically significant effect) is actually less than KTC and ITC. This is probably the most clinically relevant consideration, since the azole’s affinity for mammalian CYP3A is the primary basis for drug-drug interactions with other CYP3A-dependent compounds such as cyclosporin [47]. The potency of VRC in inhibiting CYP3A4 metabolism varies among other substrate drugs such as HIV protease inhibitors and immunosuppressants. CYP2C19 exhibits genetic polymorphism: 3-5% of Caucasians are poor metabolizers of CYPC19 substrates, while for Asian populations this is as high as 15-20% [4]. The latter such individuals should have higher VRC levels than normal metabolizers. Again, the clinical significance of such variations is unclear.

Because of such concerns, the ability of VRC to interact with other agents has been assessed both in vitro and in vivo. Drug interaction studies demonstrated that VRC may inhibit CYP3A enzymes, which in some cases may result in clinically significant drug interactions. Drug-drug interactions with other substrates of these enzymes, as well as

| Table 1: Voriconazole drug-drug interactions. |
|---|---|---|---|
| Drugs contraindicated with VRC | No dose adjustment when VRC is given with the following | Dose adjustment of VRC required | Clinical monitoring and/or dose adjustment required when given with VRC |
| Astemizole | Cimetidine | Rifabutin | Warfarin (prothrombin time) |
| Barbiturates (long acting) | Digoxin |  | Cyclosporine, tacrolimus (blood levels) |
| Carbamazepine | Macrolide |  | Sulfonylureas (glucose) |
| Cisapride | Antibiotics |  | Statins (CPR) |
| Pimozide | Prednisolone |  | Benzodiazepines |
| Quinidine | Rambutidine |  | Vinca alkaloids |
| Rifampin |  |  | |
| Sirolimus |  |  | |
| Tertfenadine |  |  | |

VRC = voriconazole
enzyme-inducers like phenytoin and rifampin, have been documented, and are detailed in Table 1 [54]. Again, the clinical importance of these interactions is unknown [31-38].

Clinical VRC drug-drug interactions have been explored extensively, in 19 studies including 365 volunteers where interactions of VRC and 20 other drugs were assessed [3]. Based on these studies, VRC drug-drug interactions were classified into the following categories: 1) contraindication (e.g. rifampin, which decreases VRC exposure, while VRC increases terfenadine levels), 2) dose adjustment of VRC or concomitant medications (e.g. concomitant use of rifabutin requires increasing the VRC dose to 5 mg/kg IV, or 400 mg orally every 12 hours), 3) monitor concentrations or effects of concomitant medications (e.g. monitor prothrombin time with warfarin), and 4) no adjustment required (e.g. digoxin).

Because of the incidence of fungal infections in patients undergoing hematogenous and solid organ transplants, interactions of VRC with commonly used transplant medications is of particular interest. Some drugs do not require dosage adjustments, including prednisolone (VRC increases its AUC by 13-34%) [31] and mycophenolate mofetil [110]. Concomitant VRC administration increases cyclosporin A and tacrolimus exposure (AUCs increasing by 1.7 and 3.2 fold, respectively), requiring close monitoring of drug levels and probable dose reduction [38 111]. Sirolimus is contraindicated because voriconazole increases its C\text{MAX} and AUC by 556% and 1,014% respectively [3].

9. Formulations, Route of Administration and Dosage

Voriconazole is available as tablets (50 mg or 200 mg) or IV preparation. The IV formulation is a lyophilize containing 200 mg VRC with 3200 mg SBECD, and is reconstituted in sterile water. The IV formulation is stable in the presence of water, sodium chloride, sodium hydroxide, carbonate, peptide, ringer's lactate, D\text{5}, and D\text{5}W solutions [3].

Dosing strategy calls for a loading (first 24 hours) and a maintenance (after first 24 hours) dose regimen. This dosing regimen targets the maximum tolerated dose and provides plasma concentrations above the MIC for common fungal pathogens. Oral dosing recommendations vary according to the patient's body weight. For patients weighing less than 40 kg, the loading dose consists of two doses of 200 mg separated by a 12-hour interval on first day, while the maintenance dose is 100 mg every 12 hours. For patients who are greater than 40 kg, the loading and maintenance doses should be 400 mg and 200 mg, respectively. The loading dose for VRC intravenous administration consists of two doses of 6mg/kg 12 hours apart, followed by a maintenance dose of 3 mg/kg every 12 hours (for serious Candida infections/empiric mycoses therapy) or 4 mg/kg every 12 hours (for IA/Scedosporium and Fusarium infections, or other serious mould infections). It is possible to increase the maintenance doses [to 4 mg/kg every 12 hours, IV: 300 mg q12 hours (patients > 40 kg); or 150 mg q12 hours (patients < 40 kg), in cases where inadequate patient response occurs. If patients are unable to tolerate the higher doses, then incremental dose reductions (1 mg/kg IV, 50 mg PO) to the original dose are recommended.

10. Clinical Efficacy

The clinical efficacy of VRC for the treatment of IA, Candida infections, and those caused by Scedosporium and Fusarium was assessed in Phase II/III clinical trials [2, 22, 51]. Additionally, VRC was recently compared with liposomal AmB for empiric antifungal treatment of patients with febrile neutropenia despite appropriate antibiotic therapy [105]. Patient populations studied have included those with bone marrow and solid organ transplants, hematogenous malignancies, HIV/AIDS, chronic granulomatous disease, and other immunocompromised states.

Denning et al. [22] conducted an efficacy and safety study of VRC in IA in an open, non-comparative multicenter study of 116 patients. Forty one percent had proven IA, while the rest had probable disease. Voriconazole dosing was as described above, and the drug was given as primary therapy in 60 patients (52%). Overall response rates were 14, 34, and 21% for complete, partial, and stable responses, respectively. Thirty-one percent of the infections failed to respond to VRC therapy. When VRC was used as primary therapy, the response rates were 17, 42, and 18% — equal to or better than that previously noted for AmB in IA. Notably, "good" responses (defined as complete or partial improvement) occurred in 60% of pulmonary or tracheobronchial disease (n = 84), 16% with brain IA (n = 19), 58% of those with hematologic disorders, and 26% of allogeneic stem cell transplant recipients. The authors concluded that VRC is efficacious in treating acute IA, and most so when used as primary therapy. Readers are encouraged to read the excellent discussion provided in the paper.

A similar, smaller, open-labeled study of the efficacy and tolerability of oral VRC (200 mg twice daily) for the treatment of chronic IA was conducted in 25 non-neutropenic patients [24]. One quarter of the patients had AIDS and 1/2 received VRC as salvage therapy, having failed IFU or AmB. The majority of patients had chronic pulmonary aspergillosis. At interim analysis, 53% of the evaluable patients (n = 19) had a response (2 complete, 5 partial, 3 stable).

Additionally, there have been a number of encouraging smaller studies and case reports. These include studies of VRC treatment of resistant or rare fungal pathogens [44, 50], VRC as salvage therapy of IA [81], use as treatment in children with invasive fungal disease, successful therapy for CNS aspergillosis [23, 44, 62, 63], disseminated
aspergillosis in chronic granulomatous disease and disseminated *Scedosporium apiospermum* (*Pseudallescheria boydii*) in a cancer patient [43]. Clinicians should be aware that Pfizer maintains an ongoing compassionate use program.

The above studies suggest VRC is an effective option for the treatment of acute and chronic aspergillosis, as well as other problematic fungal infections, with response rates comparable or superior to traditional therapy. In some cases (e.g. cerebral disease), VRC may offer a unique treatment option. Because of these results, Phase III multi-center comparative trials have been undertaken.

Three large phase III trials have confirmed VRC's status as a useful antifungal drug. The first was a multi-center, randomized, placebo-controlled, double-blinded comparison with FLC as treatment for esophageal candidiasis in immunocompromised patients [2]. Both arms showed similar efficacy and tolerability. Primary efficacy analysis of esophageal treatment, as assessed by esophagoscopy, revealed success rates (cure or improvement) of 98.3% and 95.1% with VRC and FLC, respectively. There was no significant difference between the two antifungals. Based on these findings, the authors concluded VRC, at 200 mg twice daily, is at least as effective as FLC in the treatment of biopsy-proven esophageal candidiasis in immunocompromised patients.

The second Phase III clinical trial completed evaluating VRC efficacy was a multi-center, open-label randomized comparison with AmB for the primary therapy of IA [51]. Three hundred and ninety-two patients were enrolled over a 3-year period. Patients were randomized to receive AmB 1 mg/kg/day intravenously vs. VRC 6 mg/kg every 12 hr for two doses followed by 4 mg/kg every 12 hr, and then 200 mg orally twice daily if desired. After initial randomized therapy, physicians had the option to change the treatment to any licensed antifungal therapy for IA (lipid or non-lipid AmB or ITC). At week 12, 52.8% of patients treated initially with VRC had a complete or partial response, vs. 31.6% of patients treated initially with AmB (95% CI for the difference = 32.9 to 10.4%). Survival of patients receiving VRC was 76.8% vs. 57.9% for AmB (Hazard Ratio = 0.59, with 95% CI of 0.40 - 0.88). The initial therapy was discontinued for a median of 77 days in patients on VRC vs. 11 days in those on AmB, with satisfactory endpoint outcomes in 53.5% of VRC-treated patients vs. 21.8% of AmB-treated patients (95% CI for difference = 42.6 to 21.1%). The authors concluded that VRC is more effective than AmB for IA, resulting in improved patient survival.

The third Phase III clinical trial was an international multi-center, randomized, open-label study comparing VRC with liposomal AmB (ambisome) for empiric antifungal therapy in patients with neutropenia and persistent fever despite appropriate antibiotic therapy [105]. A total of 837 patients were evaluated (415 assigned to VRC and 422 to liposomal AmB) for treatment success. The overall success rate (according to a composite score) was 26% and 35.6% for those receiving VRC and ambisome, respectively. The composite score encompassed the following: treatment was considered successful if patients did not have a breakthrough fungal infection, survived for 7 days beyond the end of therapy, did not discontinue therapy prematurely, had resolution of fever during the period of neutropenia, and were successfully treated for any base-line fungal infection. Among the five components in the composite score, the only significant difference found was in the frequency of breakthrough fungal infections. There were fewer breakthrough infections in the VRC arm compared to the AmB arm (1.9 vs. 5.2%, respectively), with the largest difference in *Aspergillus* infections (4 vs. 13 patients, respectively). Based on these findings, the authors concluded that VRC is a suitable alternative to AmB preparations for empirical antifungal therapy in patients with neutropenia and persistent fever. While a more detailed analysis of the article is beyond the scope of this review, it should be noted the FDA has expressed reservations regarding the use of VRC for this indication, at least in part due to the weighted success rates based on initial patient stratification (risk of fungal infection, + antifungal prophylaxis, and duration of neutropenia), which was not presented in the final article. The authors urge interested readers to carefully read the original paper, the FDA response, and the accompanying editorial [66].

The above studies indicate that VRC is likely at least as efficacious, and in some cases more so, than traditional therapies for serious fungal infections caused by a variety of organisms. Whether this is also the case for treatment of febrile neutropenia seems likely, but has yet to be fully determined [66]. Nonetheless, given the superiority of IV ITC and liposomal AmB [103, 109] to conventional AmB, the addition of VRC to the antifungal armamentarium may spell the end of conventional AmB use in serious infections.

11. Safety and Tolerability

The safety and tolerability of VRC was assessed in both healthy volunteers and patients enrolled in clinical trials. In general, these studies revealed that VRC has acceptable tolerability. The chief adverse effects observed included transient visual disturbance, hepatotoxicity, and skin reactions. The most frequent adverse drug reaction is visual disturbance, described as enhanced light perception, blurred vision, photophobia, or color vision changes. These visual events occurred in 23%-35% of patients [3], generally occur early (within 30 minutes of dosing), and most frequently during the first week of therapy (26% of patients). The majority of these events were mild and resolve within 30 minutes. Moreover, while functional visual changes are reversible after discontinuation of VRC therapy, symptoms generally resolve even if treatment is continued [2]. In clinical trials, vis-
ual changes rarely necessitate discontinuation of the drug [21, 24, 97]. Electoretinography (ERG) has shown the retina to be the site of these effects, with decreased amplitude of ERG waveforms in humans and dogs [96]. Six and 12-month dog studies showed that no structural alterations in the retina or visual pathways occur as a result of VRC administration. No human histopathology has been found, and ocular biomicroscopy has not detected ocular lesions.

Hepatotoxicity of VRC was assessed in Phase III clinical trials [2, 51, 105] by monitoring liver function test (LFT) abnormalities, including elevations in serum alanine transaminase (ALT), aspartate aminotransferase, alkaline phosphatase and bilirubin levels. These studies showed that LFT abnormalities might be associated with higher plasma concentrations and/or doses of VRC. Twelve and 21% of subjects had abnormal ALT, and total bilirubin levels, respectively. The majority of abnormal LFTs resolved during treatment without dose adjustment or following dose adjustment, but in some cases occurred after discontinuation of therapy. In cases where discontinuation of VRC is necessary, elevations in LFTs will likely be the chief cause [21, 24, 97]. However it is important to note that there is a similar frequency of adverse hepatic events for VRC and AmB formulations. In contrast, hepatic adverse effects occurred at a greater frequency in VRC than FLC treated patients. Since VRC has been infrequently associated with serious hepatic toxicity in patients with other substantial underlying conditions, patients who develop elevated LFTs during therapy with the antifungal should be closely monitored, and discontinuation of VRC considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to the drug.

Two types of adverse skin reactions have been noted with VRC administration during pre-marketing studies: rash and photosensitivity. Rashes noted as a result of VRC include: facial and generalized erythema, exanthem, and dermatitis (including 1 case of psoriasis with eosinophilia); there have been several cases of erythema multiforme and non-fatal Stevens-Johnson syndrome. From 6 to 25% of patients on VRC experienced some form of rash, with an incidence similar to that observed for AmB formulations (e.g. 23% and 25% for VRC and liposomal AmB, respectively) [3]. It is important to note that in Phase II clinical trials involving 271 patients (including 165 HIV+ patients, who are at higher risk of drug rashes), only 1 withdrew from treatment due to an adverse skin reaction [21, 24, 97]. The incidence of rash appears comparable with that of FLC [2]. Photosensitivity occurred at a much lower level than rash (between 1-2 %), and was more frequently observed in patients receiving greater than 12 consecutive weeks of VRC therapy [3]. Since photosensitivity occurred on light-exposed areas of the skin, it is recommended that patients avoid strong sunlight when taking VRC, as well as taking other appropriate measures (including the use of sunscreen and appropriate clothing).

Another area of potential side effects is cardiac, particularly arrhythmias. Other azoles have been implicated in long QT syndromes, particularly KTC, through its inhibition of the hepatic CYP3A4 iso-enzyme [71]. In studies comparing VRC with KTC, the former showed minimal changes in the corrected QT interval (QTc), with no patients having QTc increases greater than 60 msec [3]. There appears to be no increase in QTc changes despite increasing drug doses. In pre-clinical trials, there has been one episode of sudden cardiac death after VRC infusion. While the sponsor could not exclude the contribution of VRC to this event, it is worth noting that the patient had previous dilated cardiomyopathy and arrhythmias likely due to idarubicin therapy. In summary, while VRC does not appear to cause significant changes in QTc, due to the drug's effects on the CYP3A4 iso-enzyme, it would likely be prudent to avoid co-administering other drugs (e.g. astemizole and cisapride) which have the potential to cause QT prolongation.

Finally, azoles have been shown to be teratogenic in animal studies. In rats, high doses of VRC (60 mg/kg/day) gave class-related teratogenicity, and there may be effects at lower dose levels. Until more information is available, when given VRC, women of childbearing potential should use contraception; pregnant women should only be administered the drug if the benefits clearly outweigh the risks [3].

12. CONCLUSIONS

It is clear that we are entering a new era in antifungal therapy. The utility of triazole agents is only now becoming fully apparent, with the extension of their activity to a broad spectrum of organisms, as well as fungicidal activity against moulds, as evidenced by VRC. In the case of VRC, in vitro activity clearly extends to in vivo efficacy, in both animals and man. Voriconazole shows particular promise in treating resistant candidiasis and invasive aspergillosis as well as *Scedosporium* and *Fusarium* infections. In this role, it exhibits less toxicity than conventional agents, with potentially more efficacy. Importantly, it also offers a unique hope in the therapy of previously untreatable infections, for example, invasive CNS aspergillosis.

REFERENCES


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1. Introduction

The role of potassium in the regulation of cell membranes has been extensively studied. Potassium is known to play a crucial role in maintaining the osmotic balance and pH homeostasis in cells. It is also involved in the regulation of nerve and muscle functions. This study aims to further explore the role of potassium in various physiological processes.

2. Methods

This research was conducted using a combination of in vitro and in vivo experiments. The in vitro experiments involved measuring the potassium levels in various cell lines under different conditions. The in vivo experiments were conducted on animal models to observe the effects of potassium on physiological functions.

3. Results

The results indicated a significant increase in potassium levels in the experimental groups compared to the control group. These findings suggest a potential role of potassium in the treatment of certain diseases.

4. Discussion

The observed changes in potassium levels raise important questions about the potential therapeutic applications of potassium supplementation. Further studies are needed to fully understand the mechanisms underlying these findings.

5. Conclusion

In conclusion, this study highlights the importance of potassium in cell functions and suggests potential therapeutic applications. Further research is needed to explore the full extent of potassium's role in various physiological processes.


110. Wood N, Abel S, Fielding A, Nichols DJ, Bygrave E (2001) Voriconazole does not affect the pharma­cokinetics of mycophenolic acid. 41st Interscience
Conference on Antimicrobial Agents and Chemotherapy, Abstr. #A-24. Chicago, American Society for Microbiology


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