Objective: To investigate the penetration of voriconazole, a new-generation triazole antifungal agent, into the vitreous and aqueous humor after oral administration.

Methods: A prospective, nonrandomized clinical study included 14 patients scheduled for elective pars plana vitrectomy surgery between December 1, 2002, and February 28, 2003, at the Cullen Eye Institute, Houston, Tex. Aqueous, vitreous, and plasma samples were obtained and analyzed from 14 patients after oral administration of two 400-mg doses of voriconazole taken 12 hours apart before surgery. Assays were performed by means of high-performance liquid chromatography.

Results: Mean±SD voriconazole concentrations in plasma (n=14), vitreous (n=14), and aqueous (n=11) were 2.13±0.93 µg/mL, 0.81±0.31 µg/mL, and 1.13±0.57 µg/mL, respectively. Mean±SD sampling times after oral administration of the second voriconazole dose for plasma, vitreous, and aqueous were 2.4±0.6 hours, 3.0±0.5 hours, and 2.9±0.5 hours, respectively. The percentages of plasma voriconazole concentration achieved in the vitreous and aqueous were 38.1% and 53.0%, respectively. Mean vitreous and aqueous minimum inhibitory concentrations for 90% of isolates (MIC90) were achieved against a wide spectrum of yeasts and molds, including Aspergillus species and Candida species, along with many other organisms.

Conclusions: Orally administered voriconazole achieves therapeutic aqueous and vitreous levels in the noninflamed human eye, and the activity spectrum appears to appropriately encompass the most frequently encountered mycotic species involved in the various causes of fungal endophthalmitis. Because of its broad spectrum of coverage, low MIC90 levels for the organisms of concern, good tolerability, and excellent bioavailability with oral administration, it may represent a major advance in the prophylaxis or management of exogenous or endogenous fungal endophthalmitis.


Fungal endophthalmitis can be either exogenous or endogenous in origin. Exogenous fungal endophthalmitis occurs primarily in individuals by 3 principal causes: surgery, contiguous spread from an external ocular infection, and trauma. In all cases, fungus gains entry into the anterior chamber, the vitreous, or both. Progression of the infection is dependent on the size of the inoculum at the time of injury, the growth rate of the fungus, and the status of the host’s immunologic system.1,2 Endogenous fungal endophthalmitis occurs primarily in patients who are in a compromised state of health. Risk factors include the use of long-term and broad-spectrum antibiotics, corticosteroids and cytotoxic agents, indwelling intravenous catheters and hyperalimentation, and intravenous narcotic drugs. The increased survival of patients with debilitating diseases and AIDS has also contributed to the increasing incidence of endogenous fungal endophthalmitis. Spread of fungus to the eye characteristically occurs after fungemia, usually caused by a yeast. The most commonly encountered yeast is Candida species (primarily Candida albicans). The major filamentous fungus seen in endogenous endophthalmitis is Aspergillus species.1 The incidence of endogenous fungal endophthalmitis has increased substantially during the past few decades and has been reported to vary between 2% and 45% among patients with systemic fungal infection.3,5

Although fungal endophthalmitis is rare in the grand scheme of intraocular infection, it remains an important clinical problem in ophthalmology because of the potentially devastating consequences resulting from these infections. In addition, ocular fungal infections have traditionally been very difficult to treat because of limited therapeutic options both sys-
In the past few years, there have been major strides in the development of antifungal agents, and their potential use in the treatment of fungal endophthalmitis needs to be explored. The new-generation triazoles, such as voriconazole, posaconazole, and ravuconazole, represent advances in the evolution of the triazole antifungal class and have been developed to address the increasing incidence of fungal infections and the limitations of the currently available agents.

Voriconazole is a triazole antifungal agent and is a second-generation synthetic derivative of fluconazole. It was developed by Pfizer Pharmaceuticals Group (Pfizer Inc, New York, NY) as part of a program designed to enhance the potency and spectrum of activity of fluconazole. Voriconazole differs from fluconazole by the addition of a methyl group to the propyl backbone and by the substitution of a triazole moiety with a fluoropyrimidine group, resulting in a marked change in activity (Figure 1). Voriconazole has 96% oral bioavailability and reaches peak plasma concentrations 2 to 3 hours after oral dosing. Protein binding is moderate at 58%, with wide distribution of the agent throughout the body into many tissues and fluids. Previous in vitro studies have shown voriconazole to have a broad spectrum of action against Aspergillus species, Blastomyces dermatitidis, Candida species, Paecilomyces lilacinus, Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum, Penicillium species, Scedosporium species, Curvularia species, and others.

We chose to study the intraocular penetration of orally administered voriconazole in humans for 3 reasons. First, older-generation triazoles such as fluconazole have been shown to achieve significant levels in the vitreous after oral administration in the noninflamed eye. Second, whole-body autoradiography studies in rats showed that voriconazole is very highly concentrated in the retina, second only to levels observed in the liver. Third, the MICs for 90% of isolates (MIC90) of voriconazole against the pathogens most commonly responsible for exogenous and endogenous fungal endophthalmitis were generally lower than those for the other antymycotic agents we surveyed (Table 1).

**METHODS**

This study was carried out with the approval of the Baylor College of Medicine Institutional Review Board. Fourteen adult patients, aged 30 to 87 years (mean, 58 years), undergoing elective pars plana vitrectomy surgery between December 1, 2002, and February 28, 2003, at the Cullen Eye Institute, Houston, Tex, were included in the study. Exclusion criteria included the following: age younger than 18 years, known sensitivity to triazole agents, use of any other antibiotic(s) or antifungal(s) in the preceding 3 weeks, pregnancy or current breastfeeding, fresh vitreous hemorrhage as an indication for vitrectomy (less...
Ventricular penetration of voriconazole is 0.81 ± 0.31 µg/mL; aqueous penetration, 1.13 ± 0.57 µg/mL. Data are from Marco et al.19 Ghannoum and Kahn,20 and Espinel-Ingroff et al.24

†Typically susceptible to voriconazole with the exception of a single isolate that demonstrated a minimum inhibitory concentration of greater than 16.0 µg/mL.22

Table 1. In Vitro Susceptibilities of Voriconazole Showing Minimum Inhibitory Concentrations at Which 90% of Isolates are Inhibited

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Concentration, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeast and yeast-like species</td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>0.06</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>0.12 to 0.25</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>0.25 to 16.0</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>0.06 to 0.25</td>
</tr>
<tr>
<td>Dimorphic fungi</td>
<td></td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>0.25</td>
</tr>
<tr>
<td>Coccioidioides immitis</td>
<td>0.25</td>
</tr>
<tr>
<td>Histoplasma capsulutin</td>
<td>0.25</td>
</tr>
<tr>
<td>Penicillium marnefei</td>
<td>0.03</td>
</tr>
<tr>
<td>Dimorphic fungi</td>
<td></td>
</tr>
<tr>
<td>Curvularia</td>
<td>0.06 to 0.25</td>
</tr>
<tr>
<td>Scedosporium apiospermum</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Therapy for fungal infections can be difficult and prolonged. The difficulty in treatment is due to a combination of the growth characteristics of fungi, the limited availability of effective antifungal agents, and the poor tissue penetration of previously investigated agents. The most important therapeutic principle in endophthalmitis is early diagnosis and correct identification of the fungus, as early treatment is more likely to yield a better visual outcome.27

One of the most common current treatment regimens for fungal endophthalmitis involves the use of intravenous amphotericin B. While this antymycotic agent is effective in treating disseminated fungal infection, it has very limited intraocular penetration.17,18 Therefore, vitrectomy with intravitreal amphotericin B has been the most current treatment for fungal endophthalmitis.1 The value of intravitreal amphotericin B has not been proven,

**RESULTS**

Indications for operation in the 14 patients were as follows (Table 3): epiretinal membrane (9 patients), macular hole (2), traction retinal detachment (2), and dense white cataract (1).

Mean voriconazole concentrations in plasma (n=14), vitreous (n=14), and aqueous (n=11) were 2.13±0.93 µg/mL, 0.81±0.31 µg/mL, and 1.13±0.57 µg/mL, respectively. Mean sampling times after oral administration of the second voriconazole tablets for plasma, vitreous, and aqueous were 2.4±0.6 hours, 3.0±0.5 hours, and 2.9±0.5 hours, respectively (Table 3). The percentages of plasma voriconazole concentration achieved in the vitreous and aqueous were 38.1% and 53.0%, respectively. Positive correlations were observed between plasma and vitreous concentrations of voriconazole (Figure 2; R=0.64). A similar correlation was observed between plasma and aqueous concentrations of voriconazole as well (Figure 3; R=0.61).

Two of the 14 patients were diabetic. The mean voriconazole concentrations in the plasma and vitreous for these 2 patients were 2.80±0.59 µg/mL and 0.77±0.24 µg/mL, respectively. These levels were not significantly different from those of the 12 nondiabetic patients, whose plasma and vitreous concentrations were 2.01±0.94 µg/mL and 0.82±0.33 µg/mL, respectively (P=.28 and P=.86, respectively).

Five of the 14 patients had pseudophakic eyes. The mean voriconazole concentrations in the plasma, vitreous, and aqueous for these 5 patients were 2.13±0.68 µg/mL, 0.90±0.38 µg/mL, and 1.25±0.71 µg/mL, respectively. These levels were not significantly different from those of the 9 patients whose eyes had phakic status, whose plasma, vitreous, and aqueous concentrations were 2.12±1.08 µg/mL, 0.76±0.28 µg/mL, and 1.03±0.48 µg/mL, respectively (P=.99, P=.44, and P=.56, respectively).

No serious adverse reactions were attributed to voriconazole. Two patients complained of transient visual blurring occurring approximately 30 minutes after taking the first voriconazole dose (patients 6 and 8; Table 3).

**COMMENT**

Therapy for fungal infections can be difficult and prolonged. The difficulty in treatment is due to a combination of the growth characteristics of fungi, the limited availability of effective antifungal agents, and the poor tissue penetration of previously investigated agents. The most important therapeutic principle in endophthalmitis is early diagnosis and correct identification of the fungus, as early treatment is more likely to yield a better visual outcome.27

One of the most common current treatment regimens for fungal endophthalmitis involves the use of intravenous amphotericin B. While this antymycotic agent is effective in treating disseminated fungal infection, it has very limited intraocular penetration.27,28 Therefore, vitrectomy with intravitreal amphotericin B has been the most current treatment for fungal endophthalmitis.1 The value of intravitreal amphotericin B has not been proven,
and toxicity questions do remain.\textsuperscript{28} In addition, if mistakes are made in preparing dilutions or if the preparation is injected into an air-filled eye, there is the potential for serious toxic adverse effects to the retina. For these reasons, Christmas and Smiddy\textsuperscript{29} investigated alternate management techniques for fungal endophthalmitis to avoid the risk of toxic adverse effects to the retina. They found that pars plana vitrectomy with systemic fluconazole successfully treated \textit{Candida} endophthalmitis in several patients. Since their report in 1996, there have been major advances in the development of antifungal agents. If the use of systemic antifungal agents is to be considered for the prophylaxis, or as an adjunct in the management, of fungal endophthalmitis, a systemic agent must

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|}
\hline
\textbf{Drugs Contraindicated} & \textbf{Dose Adjustment} & \textbf{Clinical Monitoring and/or Dose Adjustment} & \textbf{Dose Adjustment of Voriconazole} \\
\textbf{With Voriconazole} & \textbf{of Voriconazole Required} & \textbf{Required When Given With Voriconazole} & \textbf{and/or Co-administered Drug Required} \\
\hline
Astemizole & Rifabutin & Warfarin (prothrombin time) & Omeprazole (half dose of omeprazole, no change of voriconazole dose) \\
Barbiturates & Rifampin & Cyclosporine (blood levels) & Phenytoin (monitor blood levels and adjust voriconazole dose) \\
Carbamazepine & & Tacrolimus (blood levels) & \\
Cisapride & & Statins (creatinine phosphokinase) & \\
Pimozide & & Benzodiazepines (toxicity) & \\
Quinidine & & Vinca alkaloids (toxicity) & \\
Rifampin & & Sulfonlureas (glucose) & \\
Sirolimus & & & \\
Terfenadine & & & \\
\hline
\end{tabular}
\caption{Voriconazole Drug-Drug Interactions*}
\end{table}

*Data from Ghannoum and Kuhn.\textsuperscript{23}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|}
\hline
\textbf{Patient No./Age, y} & \textbf{Hours From Second Dose} & \textbf{Indication for Surgery} & \textbf{Voriconazole, µg/mL} \textbf{Plasma} & \textbf{Aqueous} & \textbf{Vitreous} \\
& to Vitreous Sample & & & & \\
\hline
1/63 & 3.8 & TRD & 3.22 & 1.84 & 0.94 \\
2/50 & 3.5 & ERM & 1.72 & 0.69 & 0.47 \\
3/71 & 3.0 & ERM & 2.20 & 2.38 & 1.39 \\
4/60 & 2.0 & TRD & 2.38 & NA\textsuperscript{*} & 0.80 \\
5/41 & 2.7 & ERM & 1.52 & 0.87 & 0.65 \\
6/58 & 2.3 & MH & 2.64 & 1.19 & 0.75 \\
7/87 & 2.8 & ERM & 2.57 & 1.00 & 1.02 \\
8/56 & 3.3 & ERM & 3.85 & NA\textsuperscript{*} & 1.27 \\
9/50 & 2.1 & ERM & 0.96 & 0.43 & 0.35 \\
10/73 & 3.2 & ERM & 2.28 & 1.23 & 1.00 \\
11/40 & 3.3 & MH & 3.21 & NA\textsuperscript{*} & 0.92 \\
12/73 & 3.0 & ERM & 1.06 & 1.23 & 0.81 \\
13/66 & 3.3 & ERM & 1.20 & 1.05 & 0.84 \\
14/43 & 3.4 & WC & 0.95 & 0.48 & 0.33 \\
\hline
\end{tabular}
\caption{Patient Characteristics}
\end{table}

Abbreviations: ERM, epiretinal membrane; MH, macular hole; NA, not available; TRD, traction retinal detachment; WC, white cataract.

*Indicates sample not taken because of risk of compromising surgical procedure.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Voriconazole levels obtained in plasma and vitreous (\(r=0.64\)).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Voriconazole levels obtained in plasma and aqueous (\(r=0.61\)).}
\end{figure}
be found with the highest possible intraocular penetration, as well as the lowest MIC90 for the organisms of concern. Given our findings, we believe that voriconazole may represent a major advance in this regard (ie, in vitro potency of voriconazole against yeasts was 60-fold higher than that of fluconazole)24.

We are aware of 4 published reports of successful treatment of fungal endophthalmitis with the new-generation triazoles. The first report involves a patient with exogenous endophthalmitis from *Fusarium solani* infection secondary to a severe keratitis. Because of a lack of response to conventional therapy, voriconazole treatment was started systemically, topically, and by intracameral injection. The patient’s clinical situation steadily improved, and voriconazole treatment was stopped after 8 weeks, with complete resolution of infection.30 More recently, Garbino and colleagues31 described an immunocompetent woman who developed *Fusarium* endophthalmitis secondary to complicated cataract surgery. The patient’s clinical situation had deteriorated despite treatment with several agents in addition to oral itraconazole and intracameral fluconazole. The patient’s treatment regimen was switched to voriconazole, 400 mg every 12 hours, when cultures showed that the organism was highly susceptible to this new triazole. During the course of 3 months, the patient’s condition steadily improved, with complete resolution of infection. Sponsel and colleagues32 described a patient with exogenous *P. lilacinus* endophthalmitis secondary to complicated cataract surgery. She was treated with topical antibiotics for concurrent bacterial keratitis, as well as topical and intravenous amphotericin B, natamycin, and ketoconazole. Despite this intensive regimen, the infection spread into the anterior chamber. Therapy was switched to the new triazole posaconazole (oral and topical) after cultures demonstrated amphotericin B–resistant *Fusarium* species. Within 1 week of this new therapy there was significant clearing of the cornea, and 3 months later there was no evidence of infection. Finally, Kim and colleagues33 recently reported their experiences treating a 65-year-old woman with refractory *A. fumigatus* scleritis and a nodular epibulbar abscess caused by scleral buckle infection. Oral and topical itraconazole, ketoconazole, and amphotericin B treatment only resulted in progression of infection during the course of 4 months. All therapy was discontinued and treatment with oral voriconazole, 200 mg twice a day, was begun. After 1 week of treatment, ocular tenderness disappeared and the infection resolved steadily thereafter.

Because of the study design, it is not known whether sampling occurred during voriconazole peak or trough intraocular levels. This investigation, however, provides proof of principle that therapeutic intraocular levels of orally administered voriconazole can be achieved in the noninflamed human eye. Table 1 compares the vitreous and aqueous concentrations of voriconazole obtained in this study with previously established in vitro MIC90 data.20,23,24 Included in this table are organisms that have been reported in the ophthalmic literature to cause fungal infections and for which in vitro MIC90 data were available. *Candida tropicalis* is generally susceptible to voriconazole, with the exception of a single isolate that demonstrated an MIC of more than 16.0 μg/mL.22 In addition, voriconazole was unable to achieve intraocular levels effective against *Fusarium* species. This is not to suggest that voriconazole may not be of therapeutic value for fungal endophthalmitis because of these organisms; a previous study suggests that intraocular penetration of systemic agents may be higher in an eye that has sustained trauma, is infected, or is inflamed.33 This may be owing to disruption of the blood-ocular barrier and could help explain the beneficial effects of voriconazole and posaconazole against *Fusarium* species in the previously mentioned case reports.

Voriconazole is very well tolerated, with most adverse reactions described as mild. The primary adverse effects observed include transient visual disturbance, hepatotoxicity, and skin reactions. Visual disturbance is the most frequent drug reaction, observed in 23% to 35% of individuals, and has been described as enhanced light perception, color vision change, and blurring. These symptoms typically occur 30 minutes after administration and during the first week of therapy. Resolution of these symptoms occurs within 30 minutes after onset, and symptoms generally resolve even with continued therapy.21 Two patients in our study reported these symptoms after taking their first voriconazole dose (patients 6 and 8; Table 3). Decreased-amplitude waveforms on electroretinograms in humans and dogs suggest that the retina is the tissue causing these effects.21 In addition, studies in dogs have shown that no structural alterations in the retina or visual pathways occur as a result of voriconazole administration. Fortunately, there are no known long-term ocular side effects of voriconazole use.22 Voriconazole is metabolized primarily by the hepatic cytochrome P450 isozymes CYP2C19, CYP2C9, and CYP3A4.23 Therefore, there are several drug-drug interactions, as described in Table 2. Hepatotoxicity has been known to occur with voriconazole use;23 therefore, monitoring of hepatic functions is recommended. Rash occurs with a frequency of about 6% to 25%.23 In addition, photosensitivity has been noted during voriconazole treatment, and protective measures are recommended (avoiding strong sunlight and covering exposed skin areas).23 Finally, triazoles in general have been shown to be teratogenic in animal studies.23 Therefore, until data on voriconazole from humans are available, it is recommended that women of childbearing potential use contraception. Voriconazole use in pregnant women should be considered only if the benefits outweigh the risks.23 There are certain dosing modifications required in special clinical circumstances (ie, renal impairment), and we advise reviewing the voriconazole package insert before initiating systemic voriconazole therapy.

The recommended oral dosage of voriconazole is one 200-mg tablet every 12 hours. In certain clinical situations, a loading dose of 400 mg every 12 hours for 1 day may be considered. In our study design, we chose to use the loading dose regimen before sample collection to achieve peak plasma concentrations more rapidly (when oral loading dose regimens are administered to healthy subjects, peak plasma concentrations close to steady state are achieved within the first 24 hours of dosing). In severe ocular mycotic infection, use of this loading dose regimen may be considered to help achieve peak plasma concentrations of voriconazole more rapidly.
The realization that voriconazole may have important ocular clinical application is not novel. In a recent study by Zhou and colleagues, albino rabbits were treated with topical eyedrops of voriconazole at a “low dose” (50 µg/mL) and a “high dose” (100 µg/mL) twice a day for 11 days. Aqueous humor samples were then obtained though a paracentesis site with a 30-gauge needle attached to a syringe and later analyzed by means of liquid chromatography–mass spectrometry with electrospray ionization. Impressive voriconazole concentrations were found in the aqueous humor: 7.29±5.84 µg/mL in the low-dose group (n=4) and 14.56±12.90 µg/mL (n=7) in the high-dose group. In addition, Zhou et al discovered that voriconazole penetrates the normal eye without metabolic modification. That study demonstrated aqueous concentration of voriconazole severalfold higher than the levels observed in our study. There is an explanation for this large discrepancy; Zhou and associates’ investigation was an animal study and the route and duration of therapy were very different from those in our study. In addition, penetration of topical voriconazole into the vitreous was not investigated; therefore, no conclusions can be drawn regarding its use in open-globe trauma or fungal endophthalmitis involving the posterior segment. Given Zhou and coworkers’ findings, however, further investigation of topical voriconazole is warranted to determine whether the human eye can tolerate such a formulation.

In summary, orally administered voriconazole achieves therapeutic aqueous and vitreous levels in the noninflamed human eye, and the activity spectrum appears to appropriately encompass the most frequently encountered fungal species involved in the various causes of exogenous and endogenous fungal endophthalmitis. In addition, oral voriconazole may present an alternate management technique for fungal endophthalmitis by which the risk of toxic adverse effects to the retina associated with intravitreal amphotericin B injection can be avoided. Because of its broad spectrum of coverage, low MIC90 levels for the organisms of concern, good tolerability, and excellent bioavailability with oral administration, it may represent a major advance in the prophylaxis or management of fungal endophthalmitis.

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