An Update on Voriconazole in Ophthalmology

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Abstract

Ocular mycosis is one of the leading causes of corneal blindness. The range of common antifungal agents available for ocular mycosis remains inadequate and is generally associated with poor clinical outcomes. Voriconazole is a newer generation triazole antifungal agent, only marketed in systemic formulation, with broad-spectrum activity and a high intracellular penetration. Voriconazole has demonstrated effectiveness against ocular mycosis. This review article is aimed at providing comprehensive information about the uses of voriconazole in ophthalmology in different scenarios. Off label preparation and different routes of administration like intrastromal, intracameral and intravitreal etc. been described along with case reports and relevant studies. It has been demonstrated in many case reports that voriconazole has been used as a stand alone therapy, as a second line of drug in unresponsive cases and also as an adjunctive drug along with other antifungals.

Keywords: voriconazole, fungal keratitis, efficacy, intrstromal

Introduction

The 1990s witnessed an expansion of the antifungal armamentarium to include two new azole agents, namely fluconazole and itraconazole. These agents changed our approach in treating many fungal infections. However, neither was an ideal agent. Fluconazole had a limited spectrum of antifungal activity and resistance was soon noted in immunosuppressed hosts who received long term treatment. Itraconazole was plagued by absorption problems. Second-generation triazole agents have been in development for the past decade. The first of these newer agents to receive approval from the US Food and Drug Administration (FDA) is voriconazole.1

Fungal eye infections, common in temperate climates, have been notoriously difficult to diagnose and treat. Current treatment options are far from optimal. New generation triazoles, including voriconazole, have been shown in laboratory studies and clinical experience to have very good safety profiles with fewer side effects.

Voriconazole is a triazole having a structure similar to fluconazole with the addition of a methyl group to the propyl backbone and the replacement of a triazole moiety with a fluoropyrimidine group but with increased activity in vitro, an expanded spectrum, and poor aqueous solubility.2 (Figure 1).

Mechanism of Action of Voriconazole

The major effect of imidazoles and triazoles on fungi is inhibition of 14-sterol demethylase, a microsomal Cytochrome Peroxidase (CYP). Imidazoles and triazoles thus impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14-methylsterols. These methylsterols may disrupt the close packing of acyl chains of phospholipids, impairing the functions of certain membrane-bound enzyme systems, thus inhibiting the growth of the fungi.2

Pharmacokinetics

Absorption, Distribution, and Excretion

Oral bioavailability is 96% and protein binding 56%. Volume of distribution is high (4.6 L/kg), with extensive drug distribution in tissues. Metabolism occurs through cytochrome peroxidase. Less than 2% of parent drug is recovered from urine, although 80% of the inactive metabolites are excreted in the urine. The oral dose does not have to be adjusted for azotemia or hemodialysis. Plasma elimination t ½ is 6 hours. Patients with mild-to-moderate cirrhosis should receive the same loading dose of voriconazole but half the maintenance dose.2

The intravenous formulation of voriconazole contains sulfobutyl ether-cyclodextrin (SBEDC). When voriconazole
is given intravenously, SBECID is excreted completely by the kidney. Significant accumulation of SBECID occurs with a creatinine clearance <50 mL/minute. Because toxicity of SBECID at high plasma concentrations is unclear, oral voriconazole is preferred in azotemic patients.²

**Spectrum of Activity**

Voriconazole is potent against a wide spectrum of fungi, namely, Candida albicans, Candida parapsilosis, Candida tropicalis, Aspergillus fumigatus, Aspergillus flavus, Fusarium solani, and other less common pathogens from the Paecilomyces, Histoplasma, Scedosporium, Curvularia, and Acremonium species. In a study by Marangon et al, in which the in vitro susceptibility of common pathogens to voriconazole was compared with that for amphotericin B, fluconazole, itraconazole, and ketoconazole, voriconazole demonstrated the lowest MIC₉₀, as shown in Table 1. The in vitro MICs of voriconazole is highest against Fusarium solani and least against Candida albicans as shown in Table 2.³,⁴

**Intraocular penetration of systemic voriconazole**

In a prospective clinical study, Hariprasad et al demonstrated that systemic voriconazole achieved good penetration into the aqueous and vitreous humors of the human eye. Although it has good intraocular penetration, systemic voriconazole may result in side effects, however most of them are reversible.⁵

**Eye drops and Topical formulations**

**Aqueous humor concentration in Non - keratitis and keratitis patients**

Three studies have investigated voriconazole penetration through the human cornea (non-keratitis) into the aqueous humor. Two of them investigated 1% voriconazole eye drops and one investigated 2% voriconazole eye drops.⁶,⁷ The sixth hourly and hourly dosing, voriconazole concentrations in the aqueous humor were studied which suggested that six-hourly dosing of 1% voriconazole eye drops may be ineffective. Samples taken after hourly dosing were collected approximately one hour after the last dose but the aqueous humor concentrations achieved were not sufficiently high to be effective against all common pathogenic fungi. Although voriconazole concentrations were detected in the aqueous humor after topical administration of voriconazole eye drops, this may not necessarily correlate with efficacy in the clinical setting of fungal keratitis.⁸ Well-designed clinical studies of voriconazole eye drops in patients with active fungal keratitis are difficult to perform and therefore such studies are lacking. The study by Al-Badriyeh et al found that the concentration of voriconazole in the aqueous humor resulting from the 2% voriconazole eye drops was not significantly different from that reported for the 1% solution. In three of the clinical studies of Vemulakonda et al, Lau et al and Al-Badriyeh et al both 1% and 2% voriconazole eye drops were well tolerated with no side effects reported.⁹,¹⁰ To date, the penetration of topical voriconazole eye drops in patients with infective keratitis has been reported only twice, in the form of case reports. In these studies good aqueous humor concentrations were achieved following hourly dosing of topical 1% voriconazole and provided enough support for benefit of using voriconazole eye drops.¹¹,¹²

**Stability of voriconazole eye drops**

According to the stability study by Al-Badriyeh et al, 1% voriconazole eye drops, prepared in sterile benzalkonium chloride 0.01% solution, were stable for at least 14 weeks when stored at 2-8°C, while 2% voriconazole eye drops, also prepared in sterile benzalkonium chloride solution, were stable for 16 weeks at 2-8, 25, and 40°C.¹³ This was consistent with the stability study by Dupuis et al, where 1% voriconazole eye drops, prepared in sterile water for injection, were stable for at least four weeks when stored at 4°C.¹⁴ Such long-term stability data will help minimize wastage and is pivotal to facilitate the use of the eye drops in the outpatient setting.

**Drug Interactions**

Voriconazole is metabolized by, and inhibits, CYPs. The major metabolite of voriconazole, the voriconazole N-oxide, also inhibits these CYPs. Inhibitors or inducers of these CYPs may increase or decrease voriconazole plasma concentrations.

| Organism                  | MIC₉₀ (μg/mL) |
|---------------------------|--------------|
| Candida albicans          | 0.06         |
| Candida parapsilosis      | 0.12-0.25    |
| Candida tropicalis        | 0.25-16.0    |
| Cryptococcus neoformans   | 0.06-0.25    |
| Aspergillus fumigatus     | 0.50         |
| Aspergillus flavus        | 0.50         |
| Fusarium spp.             | 0.25-8       |
| Fusarium solani           | 2            |
| Paecilomyces lilacinus    | 0.50         |
| Acremonium alabamensis    | 0.25         |
| Blastomyces dermatitidis  | 0.25         |
| Coccidioides immitis      | 0.25         |
| Histoplasma capsulatum    | 0.25         |
| Penicillium marneffei     | 0.03         |
| Cuvularia spp.            | 0.06-0.25    |
| Scedosporium spp.         | 0.5          |
| Scedosporium apiospernum  | 0.5          |

**Table 1. In vitro minimum inhibitory concentration (MIC₉₀) of different antifungal agents³**

| Antifungal Agent | Aspergillus spp. (μg/mL) | Candida spp. (μg/mL) | Fusarium spp. (μg/mL) |
|------------------|--------------------------|----------------------|-----------------------|
| Voriconazole     | 0.5                      | 0.016                | 2                     |
| Amphotericin B   | 2                        | 0.5                  | 2                     |
| Itraconazole     | 1                        | 0.256                | >16                   |
| Fluconazole      | >256                     | 0.5                  | >256                  |
| Ketoconazole     | 4                        | 0.032                | >16                   |

**Table 2. In vitro minimum inhibitory concentration (MIC₉₀) of different organisms with voriconazole⁴**

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concentrations, respectively. In addition, there is potential for voriconazole and its major metabolite to increase the plasma concentrations of other drugs metabolized by these enzymes like omeprazole, sirolimus, digoxin, phenytoin and so on. The dose of omeprazole should be reduced by half. As the sirolimus AUC increases 11-fold when voriconazole is given, co-administration is contraindicated.\(^2\)

**Side effects**

Although voriconazole is generally well tolerated, occasional cases of hepatotoxicity have been reported, and liver function should be monitored. Voriconazole, like some other azoles, causes changes in electrocardiographic wave forms. Patients must be warned about possible visual effects. Transient visual or auditory hallucinations are frequent after the first dose, usually at night and particularly with intravenous administration. Symptoms diminish with time. Patients receiving their first intravenous infusion have had anaphylactoid reactions, with faintness, nausea, flushing, feverishness and rash.

**Formulations and Routes of Administration**

Voriconazole is used in different routes and formulations as eye drops, intrastromal, intracameral and intravitreal injection and also systemically by oral route and intravenous routes.

**Systemic Route**

I.V. Voriconazole (VFEND, Pfizer, Newyork State, USA) is a white lyophilized powder containing 200 mg voriconazole and 3200 mg sulfobutyl ether beta-cyclodextrin sodium in a 30 mL Type I clear glass vial.\(^15\)

Vials containing 200 mg lyophilized voriconazole should be reconstituted with distilled water to produce a solution containing 10 mg/mL VFEND and 160 mg/mL of sulfobutyl ether beta-cyclodextrin sodium.\(^15\)

**Oral**

VFEND Tablets contain 50 mg or 200 mg of voriconazole.\(^15\)

**Ocular route**

**Uses of Voriconazole**

1. **Fungal Keratitis**

Fungal keratitis is most common in tropical regions and developing countries, where it constitutes over 50% of keratitis. In South India, about 44% of corneal ulcers are caused by fungi.\(^17\) Corneal ulcers from fungi are most commonly associated with agricultural and outdoor activities. The filamentous fungi, Fusarium and Aspergillus species are amongst the most common.\(^18\) Fungal keratitis can involve any part of cornea and can present as epithelial defect with infiltrates, deep stromal abscess or as an endophthalmitis secondary to keratitis etc. Voriconazole has been found to be efficacious in treating all these condition, in different routes as follows

**A. Topical eye drops**

Currently, voriconazole eye drops are aseptically manufactured by diluting the IV formulation of 200 mg voriconazole. Voriconazole is a lipophilic compound with low solubility and usually is encapsulated with a β-cyclodextrin derivative in the form of lyophilized powder of cyclodextrin-voriconazole complex to make it more soluble in aqueous. The powder is reconstituted with 19 mL of distilled water for injection to produce a 20 mL aqueous voriconazole solution with concentration of 10 mg/mL (1%). This voriconazole solution is what is typically being used as eye drops.\(^7\) Voriconazole (Vozole, aurolabs, Madurai, Tamilnadu, India) contains 30 mg sterile lyophilized voriconazole powder. To get 1% powder has to be reconstituted with 3 mL distilled water.\(^19\) In the two case reports by Al-Badriyeh et al, topical 1% voriconazole eye drops were used as a standalone therapy to treat S. apiospermum keratitis and C. albicans keratitis which were unresponsive for empirical treatment.\(^20,21\) In these case reports, voriconazole eye drops were typically administered with a dosing frequency of one drop every 0.5, 1.0, or 2.0 hours for duration of one month. Increasing the concentration of voriconazole eye drops may lead to increased efficacy and/or reduced dosing frequency; however, the benefit of using concentrations greater than 1% has not been evaluated in patients with fungal keratitis. In a comparative study conducted by mycotic ulcer treatment trial group natamycin treatment was associated with significantly better clinical and microbiological outcomes than voriconazole treatment for smear-positive filamentous fungal keratitis, with much of the difference attributable to improved results in Fusarium cases and similar results were also found in another randomized trial conducted by Sharma S et al.\(^22,23\)

**B. Intrastromal route**

After administration of peribulbar anesthesia, under full aseptic conditions, the preloaded drug should be

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**Table 3. Method of dilution for intravitreal, intracameral and intrastromal preparations.**\(^16\)

| Operation                                                                 | Concentration          |
|---------------------------------------------------------------------------|------------------------|
| Add 19 ml of distilled water                                              | 200 mg in 20 ml        |
| Take 1 ml                                                                 | 10 mg in 1 ml          |
| Add 9 ml distilled water                                                  | 10 mg in 10 ml         |
| Take 0.05 ml/0.1 ml                                                       | 1 mg in 1 ml           |
| Take 0.05 ml/0.1 ml                                                       | 50 microgram/100 microgram in 0.1 ml |

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**Table 4. Routes of administration and dosage of voriconazole**

| Routes of administration | Dosage   |
|--------------------------|----------|
| Intravenous              | 6 mg/kg  |
| Oral                     | 200 mg twice daily |
| Eye drops                | 1% or 2% eye drops |
| Intrastromal             | 50-100 ug/0.1 ml |
| Intracameral             | 50-100 ug/0.1 ml |
| Intravitreal             | 50-100 ug/0.1 ml |
administered under operating microscope. With the bevel down, the needle is inserted obliquely from the uninvolved clear area to just reach the abscess at mid-stromal level (as the intended level for drug deposit). The drug then is injected and the amount of hydration of the cornea is used as a guide to assess the area covered. Once the desired amount of hydration is achieved, the plunger is withdrawn slightly to ensure discontinuation of the capillary column and thus prevent back-leakage of the drug. Five divided doses are given around the abscess to form a deposit of the drug around the circumference of the lesion. This is done in such a manner that a centripetally directed progressive wave of fluid appeared to encompass the abscess along each meridian. Circumferential injection will ensure the formation of a barrage of intrastromal voriconazole around the entire abscess. The total amount of drug injected intrastromally ranged from 0.05 ml to 0.1 ml.25 (Figure 2) Sharma N et al., demonstrated the efficacy of intrastromal voriconazole(50 μg/0.1 mL) in three eyes of three patients with deep stromal recalcitrant keratitis not responding to topical antifungal medications24 Kalaiselvi G et al., demonstrated the use of targeted delivery of voriconazole by intrastromal injection (50 μg/0.1 mL) as a safe and effective way to treat deep recalcitrant fungal keratitis.25

C. Oral
Oral voriconazole 200 mg twice daily for five to 17 weeks (mean, 10 weeks) according to the severity.24 Bunya VY et al., successfully treated nine patients with oral and topical voriconazole, refractory for standard treatment.26

D. Intracameral
Intracameral route has been shown to be effective in patients with fungal keratitis associated with fungal endophthalmitis27, the usual dose is 50-100μg/0.1mL.16 Intracameral voriconazole injection should be administered under aseptic conditions using an operating microscope. After instillation of topical proparacaine. A volume of 100 μg voriconazole in 0.1 mL is injected into the anterior chamber using a 30-gauge needle attached to a 1.0-mL regular insulin syringe Shen YC et al., in their case series of endophthalmitis following fungal keratitis, showed resolution of hypopyon, fungal web, fungal ball, and endothelial plaque after treatment with intracameral voriconazole(50 μg/0.1 mL).27

2. Acanthamoeba keratitis
Acanthamoeba keratitis has been recognized with increasing frequency of severe blinding keratitis. Contact lens use or exposure to contaminated water is most commonly associated. The interesting cases reported from India are not associated with contact lens use. Acanthamoeba castelleni is most common pathogen causing keratitis.28 Voriconazole has been found to be effective in treating acanthamoeba keratitis. Bang S et al., in their case series demonstrated use of topical voriconazole 1% as second-line treatment for acanthamoeba keratitis, unresponsive to chlorhexidine and hexamidine. Topical voriconazole 1% was administered at one hour interval along with oral voriconazole (200 mg twice daily).29 Tu YE et al., successfully treated recalcitrant, chronic acanthamoeba stromal keratitis with oral 200 mg voriconazole twice daily for 6 week as monotherapy.30

3. Fungal endophthalmitis
Fungal endophthalmitis is known to occur by both exogenous and endogenous routes. Endogenous fungal endophthalmitis represents intraocular dissemination of a systemic fungal infection. Among the different fungal species, Candida species is the most common cause of infection, followed by Aspergillus species. Risk factors include immunosuppression, intravenous drug abuse, bacterial sepsis, prolonged hyperalimentation, systemic antibiotics, corticosteroid therapy, recent abdominal surgery, malignancy, alcoholism and diabetes mellitus.31 Exogenous infections usually are secondary to trauma or surgery caused by variety of fungi, including Paecilomyces, Acremonium, and Sporothrix species. Fungal endophthalmitis is a rare complication after cataract surgery and most common causative fungal pathogens implicated include Candida species and molds such as Aspergillus and Fusarium species. Voriconazole as an intravitreal route has been shown to be effective in fungal endophthalmitis.32 Usual dosage is 50-100ug/0.1mL.36 Gonul S et al., reported a case of T.asahii endophthalmitis successfully treated with intravitreal and systemic voriconazole, along with pars plana vitrectomy and removal of the intraocular lens with entire lens capsule. They administered voriconazole (1 mg/mL topically) and intravitreal voriconazole (25 μg/0.1 mL). Intravitreal voriconazole was repeated 3 days later.31 In a retrospective study, Mithal K et al. concluded that combination of intravitreal amphotericin B and voriconazole injections could be a promising modality of treatment in the management of exogenous filamentous fungus endophthalmitis.34 Biju R et al., successfully treated a case of candida endogenous endophthalmitis with 200 mg oral voriconazole and 10 mg oral prednisolone, along with topical atropine sulphate and prednisolone acetate eye drops for three weeks.35

4. Aspergillus chorioretinitis
Aspergillus fumigatus is the most common pathogen in human aspergillosis. Aspergillus chorioretinitis is associated with disseminated aspergillosis in immunocompromised individuals or intravenous drug abusers. Vila Arteaga J et al., in their case study had a significant and rapid improvement in patient treated with single dose of injection intravitreal voriconazole (100 µg/0.1 ml) for aspergillus chorioretinitis, obviating the need for vitrectomy. Jang GJ et al, successfully treated aspergillus chorioretinitis with systemic voriconazole.

5. Fungal tunnel infections
Self-sealing sutureless wounds are almost universal in modern cataract surgery. Data on corneoscleral wound infections suggest both bacteria and fungus as etiological agents. Fungal infections of such incisions are especially difficult to treat because of poor corneal penetration of available antifungal agents and may have poor prognosis even after surgical intervention. Jhanji V et al., illustrated in their case report that both topical and oral voriconazole may be used in the treatment of recalcitrant cases of fungal tunnel infections not responding to conventional antifungal therapy. The patient was started on oral voriconazole 200 mg twice daily and topical voriconazole 1% every hour, and resolution of the ulcer was noted within three days. Jain V et al., successfully treated a case of fungal tunnel infection with intrastral voriconazole.

6. Orbital aspergillosis
Mucormycosis and Aspergillus are common pathogens causing orbital apex syndrome with predisposing conditions including diabetes mellitus, alcoholism, hematologic malignancies, and immunosuppression. Herbrecht R et al., compared the use of voriconazole and amphotericin B in treatment of extraorbital invasive aspergillosis. Patients received either intravenous voriconazole (two doses of 6 mg per kilogram of body weight on day 1, then 4 mg per kilogram twice daily for at least seven days) followed by 200 mg orally twice daily or intravenous amphotericin B deoxycholate (1 to 1.5 mg per kilogram per day), the planned duration of therapy was 12 weeks; voriconazole demonstrating 22% survival benefit. Sasindran et al., presented a case of an 8-year-old boy who developed an orbital apex syndrome after a trauma. A biopsy was obtained revealing Aspergillus flavus infection. He was successfully treated with 150 mg voriconazole b.i.d. for 12 months. Two more case reports from Japanese literature have revealed successful treatment of orbital apex syndrome caused by invasive orbital aspergillosis with voriconazole.

7. Fungal Subretinal abscess
Sub retinal abscesses are a rare occurrence. Whilst most are due to bacteria, reports of fungal subretinal abscess are extremely rare and only a handful of cases have been documented, in the setting of generalised sepsis, immunocompromised states and intravenous drug abuse. Huynh TH et al., demonstrated use of oral voriconazole in a 62-year-old woman who presented with bilateral Candida albicans subretinal abscesses secondary to chronic immunosuppression and the abscess resolved completely within four months of initial presentation. Panigrahi et al in their case report of aspergillus terreus endogenous sutureal abscess, noted successful outcome following treatment with intravitreal and systemic voriconazole.

8. Fungal Scleritis and epibulbar abscess
Fungal scleritis primarily involving sclera is extremely rare, but have been reported after trauma, retinal detachment surgery, pterygium surgery and scleral graft and successfully treated with voriconazole.

Conclusion
Voriconazole is a newer generation antifungal having broad spectrum activity and has less toxicity compared to other antifungals. Voriconazole eye drops appear to be effective when used for the treatment of fungal keratitis caused by a variety of fungi, including F. solani, C. albicans, S. apiospermum and A. niger. However in fusarium keratitis, natamycin seems to be more effective in comparison with voriconazole. It can be used as a first line therapy to treat many fungal infections related to eye both topically and systemically. It has been used as stand alone or as an adjunctive to treat acanthamoeba keratitis. In comparison with Amphotericin B, voriconazole is safer, can be repeated and is equally efficacious. However more data and long term studies are required to effectively formulate dosage, frequency and duration of the usage of voriconazole.

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