Voriconazole

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Fungal endophthalmitis, although uncommon, remains a serious ophthalmologic challenge owing to limited available treatments and potentially devastating ocular consequences. Fungal endophthalmitis can be caused either by exogenous origin, such as ocular trauma or surgery, or by endogenous infection spreading to the eye, such as those in immunocompromised patients. Until recently, intra vitreal injection of amphotericin B has been the principle treatment for fungal endophthalmitis although other potential intravitreal antifungal agents have been uninvestigated. However intravitreal amphotericin B, even at low concentrations 4.1 mg/ml or 8.3 mg/ml (5 mg or 10 mg injection into 1.2 ml of rabbit vitreous) can cause focal retinal necrosis. Furthermore, resistance to amphotericin B has been documented in a variety of human systemic fungal infections. Fluconazole, a triazole agent has been used systematically as a supplement or alternative to amphotericin B to treat fungal endophthalmitis because it can reach effective concentration in the vitreous after oral administration but it lacks a broad spectrum of coverage against many of the most commonly enumerated organisms found in fungal endophthalmitis. Thus ophthalmologists have had a very limited number of antifungal agents and the current treatment protocols for fungal endophthalmitis are far from optimal.

Recently, a new antifungal agent, Voriconazole, has been approved by the US Food and Drug Administration for systemic fungal infection.

Trade and Generic Names and General features.

Voriconazole is a second generation synthetic derivative of fluconazole and it 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.

Voriconazole is developed by Pfizer pharmaceuticals. The trade name of Voriconazole is Vfend TM.

Mechanisms of action

The structural changes in Voriconazole result in a higher affinity for the fungal 14-demethylase leading to more potent activities. Like fluconazole, Voriconazole exerts its effects primarily by inhibiting the fungal cytochrome P 450 CYPZA enzyme lanosterol 14 a – demethylase, preventing the conversion of lanosterol to ergosterol. This is turn causes depletion of ergosterol, which disrupts the integrity and function of the fungal cell membrane, eventually leading to cell lysis. Voriconazole also inhibits 24-methylene dihydrolanosterol demethylation in certain yeast and filamentous fungi, explaining its increased activities against moulds.

Susceptibility Patterns

Voriconazole has favourable invitro activity against a variety of fungi. These include Candida sp, Asperigillus sp, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immunities, Histoplasma capsulatum, Fusarium sp and Penicillium sp and Penicillium marneffei.
Voriconazole is generally considered to be a fungistatic agent against Candida sp and Cryptococcus neoformans.

Its enhanced activity against fluconazole resistant Candida krusei, Candida glabrata and Candida guilliermondii is noteworthy. Some fungi which are resistant to fluconazole and/or itraconazole may exhibit cross resistance to Voriconazole. Zygomycetes such as Mucor sp and Rhizomucor sp generate considerably high Voriconazole MICS.

**Pharmacology:**
- It has oral and i/v formulations.

Voriconazole is well absorbed orally with a bioavailability of 96%, allowing patients to be switched between intravenous and oral administration.

Being metabolized by hepatic cytochrome P450, Voriconazole interacts with some drugs. Administration is contraindicated with some drugs (such as sirolimus, rifampin, rifabutin and dose adjustments and/or monitoring are required when administered with others (including cyclosporine, tacrolimus, omeprazole and phenytoin). Voriconazole may be safely administered with cimetidine, ranitidine, indinavir, macrolide antibiotics, mycophenolate and prednisolone.

Because Voriconazole is metabolized by the liver the dose should be halved in patients with mild to moderate hepatic impairment. There is no data available for patients with severe hepatic impairment.

No dose adjustments is necessary for renal impairment or advanced age, but children seem to clear Voriconazole faster than adults and drugs levels may need monitoring.

In 2005, Voriconazole was also approved for the treatment of invasive candidiasis.

Intravitreal Voriconazole has been used for drug resistant fungal endophthalmitis. A recent report has compared the minimum inhibitory concentration (MIC) of natamycin, amphotericin and voriconazole against aspergillus species isolated from keratitis. MIC of natamycin was 32 mg/ml, amphotericin B was 2-4 mg/ml and that of Voriconazole was the lowest 0.25 – 0.5 mg/ml. It is to be noted that effectiveness of antifungal agents depends on the concentration of drug achieved locally, in practice; the topical antifungals are given at different concentrations - amphotericin B because of toxicity is prescribed at 0.15 %, Voriconazole at 1 % and natamycin at 5 %. Thus although the MIC level of natamycin is higher, it is administered at five times the strength of Voriconazole and 30 times that of amphotericin B.

Voriconazole eye drops is prepared by reconstituting lyophilized powder used for parental administration with 19 ml sterile water for injection to obtain 20 ml of 1 % solution and administered every hour round the clock initially and then gradually tapered as per the response. Voriconazole eye drops should be prepared every alternate day, stability of the solution could be extended up to 48 hours between 20°C and 8°C. For optimum intraocular drug concentration, both oral and topical administration of Voriconazole is recommended.

Studies in rats demonstrate that intravitreal Voriconazole did not cause any retinal toxicity on either ERG or histologic studies when concentrations were 25 mg/ml or less. When the intravitreal Voriconazole concentration reached 50 mg/ml or more, focal retinal necrosis was occasionally noticed on histologic examination, but ERG was not affected (because ERG is a mass electrical response from the whole retina and focal necrosis may not cause ERG abnormalities). When these results were transferred to human eyes, assuring minimal species variability, Voriconazole 100 mg may be injected into the human vitreous without causing long term ERG or histologic abnormalities, based on the fact that the average human vitreous volume is 4 ml. Voriconazole is much safer to the retina than amphotericin B because very low loses of intravitreal amphotericin B (4.1-8.3 mg/ml) cause focal retinal necrosis in rabbit studies. Since Voriconazole is superior or equal to amphotericin B for common and rare yeast and mould infections, Voriconazole should be considered as a possible first line intravitreal agent for treatment of fungal endophthalmitis. A recent case report showed that endophthalmitis caused by Fusarium solani was successfully treated with intracameral, topical and systemic Voriconazole when the endophthalmitis failed to respond to amphotericin B, fluconazole or itraconazole.

Voriconazole is active following both oral and intravenous administrations. In clinical trials, oral (200 mg twice daily) and intravenous (3-6 mg/kg every 12 hour) doses have produced favourable response. However, typical doses at individual clinical settings are not yet known. Parenteral administration can be followed by an oral course of Voriconazole therapy.
**Side Effects**

The most common side effects associated with Voriconazole include transient visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache, sepsis, peripheral oedema, abdominal pain and respiratory disorders.

Unlike most adverse effects, which are similar to otherazole antifungal agents, visual disturbances (such as blurred vision or increased sensitivity to light) are unique to voriconazole. Visual disturbance is an interesting and extensively investigated side effect of voriconazole. It seems to be due to the blockage of receptor deexcitation by Voriconazole. These visual disturbances have been reported by more than 30% of patients in clinical trials. They generally occur approximately one-half hour after administration and last approximately for 30 minutes. In some patients they may go away after continued use. Studies have shown that there is no damage to the eye or long term effect on vision. However, patients taking Voriconazole should be advised against driving at night or other potentially hazardous tasks.

Though rare, there have been cases of serious hepatic reactions during treatment with Voriconazole. Liver function tests should be evaluated at the start of and during the course of therapy.

This medication may also cause peeling of skin. It is best to apply lotion or coconut oil to help with this side effect.

**Current Status:**

Clinical use of Voriconazole was approved by FDA in May 2002. It was approved for primary treatment of acute invasive aspergillosis and salvage therapy for rare but serious fungal infections caused by the pathogens Scedosporium apiospermum and Fusarium sp. Thus intravitreal Voriconazole will offer a significant new treatment option in the management of fungal endophthalmitis.

**References**