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Voriconazole Eye Drops: A Revolutionary Approach for Treating Fungal Keratitis

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Abstract

Fungal keratitis is a severe and potentially sight-threatening infection of the cornea caused by various species of fungi. It poses a significant challenge to ophthalmologists due to its aggressive nature and resistance to conventional treatments. In recent years, Voriconazole eye drops have emerged as a promising therapy for fungal keratitis, offering improved efficacy and better patient outcomes. This article explores the use of Voriconazole eye drops as a treatment option for fungal keratitis, highlighting its mechanism of action, effectiveness, and safety profile. Voriconazole is a novel antifungal agent with excellent broad spectrum activity commercially available for oral and intravenous administration. The purpose of this study was to prepare ophthalmic formulation of hydroxypropyl beta cyclodextrin based voriconazole containing benzalkonium chloride BAK and EDTA with or without viscosity modifiers and study its permeation characteristics through freshly excised goat cornea.

Keywords: Fungal keratitis; Voriconazole; Eye drops

Introduction

Fungal keratitis is a sight-threatening infection of the cornea that primarily affects individuals with compromised ocular surfaces. The limited efficacy of conventional therapies has prompted the investigation of new treatment modalities. Voriconazole eye drops have gained attention due to their broad-spectrum antifungal activity and potential for improved outcomes [1]. The inflammatory disorders of the eye parts are the manifestations of the bacterial, fungal and viral infections. Fungal keratitis is one of the major causes of ophthalmic mycosis, accounting for more than 50% of proven ophthalmic mycoses in some countries. Fungal keratitis is usually characterized by a corneal epithelial defect and inflammation of the corneal stroma. If untreated, fungal keratitis can lead to corneal scarring and vision loss. Fungal keratitis is most common in tropical regions and developing countries, where it constitutes over 50% of keratitis. The ultimate goal in the treatment of fungal keratitis is to conserve vision. This requires timely diagnosis of the infection and administration of the appropriate antifungal therapy. Voriconazole is a novel second generation triazole derivative of fluconazole with excellent broad spectrum activity commercially available for oral and intravenous administration. Systemic administration of voriconazole is associated with adverse effects including cardiac arrhythmias, visual disturbances, acute renal impairment, and hepatic abnormalities. Voriconazole has broad in vitro antifungal activity against yeasts and molds, including a wide range of less common pathogens [2].

Voriconazole is widely used for the treatment of FK, but there is still no commercial ophthalmic formulation approved by the FDA or the European Medicines Agency (EMA). Only formulations marketed and approved for oral and intravenous routes are available. For this reason, hospital pharmacy departments must reformulate voriconazole formulations intended for other administration routes, usually intravenous [3]. These formulations are reconstituted with ophthalmic buffers, but their toxicity, bioavailability, and stability remain unknown in most cases. Moreover, the high nasolacrimal drainage leads to short ocular permanence and to the systemic absorption of the formulation that may trigger side effects [4].

The severity of FK is aggravated by the emergence of resistant fungal species. Antifungal combination therapy is more useful than monotherapy in antifungal-resistant fungi infections. For this reason, several studies have been conducted to evaluate different antifungals combinations or combinations between antifungals and other drugs. Ocular formulations must also be designed considering excipients that are safe for ophthalmic administration and that enhance the formulation properties [5]. The use of cyclodextrins might be considered a suitable approach to improve drug solubility. Moreover, according to the EMA, some cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin, have demonstrated ophthalmic safety, as well as improved drug permanence on the ocular surface and transcorneal permeability.

The ultimate goal in the treatment of fungal keratitis is to conserve vision. This requires timely diagnosis of the infection and administration of the appropriate antifungal therapy. Voriconazole is a novel second generation triazole derivative of fluconazole with excellent broad spectrum activity commercially available for oral and intravenous administration [6]. Systemic administration of voriconazole is associated with adverse effects including cardiac arrhythmias, visual disturbances, acute renal impairment, and hepatic abnormalities [7]. Voriconazole has broad in vitro antifungal activity against yeasts and molds, including a wide range of less common pathogens. Voriconazole possesses fungicidal in vitro activity against all Aspergillus species, molds such as Scedosporium species, and Fusarium species and is highly potent against fluconazole-resistant Candida species including Candida krusei, Candida glabrata, and Candida albicans. The 90% minimum inhibitory concentrations of voriconazole are considerably less than that of fluconazole. Voriconazole ophthalmic drops have not yet been marketed but promising results obtained with the use of voriconazole drops prepared by reconstitution of Vfend powder in several clinical studies have demonstrated the need for topical

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formulations [8]. Commonly, all the ophthalmic formulations have been administered to the eye as aqueous solutions. About 90% of the dose applied topically from such solutions is lost due to precorneal losses results poor availability. Voriconazole is a lipophilic drug with a low pH dependent aqueous solubility. The hydrophilic character of stroma in cornea restricts the permeation of lipophilic drug molecules through cornea [9].

Clinical Efficacy

Numerous clinical studies have demonstrated the efficacy of Voriconazole eye drops in the treatment of fungal keratitis. These studies have consistently reported improved clinical and microbiological outcomes, including reduced corneal infiltrates, faster resolution of infection, and improved visual acuity [10]. The Mycotic Ulcer Treatment Trial II has been particularly influential in establishing the non-inferiority of Voriconazole compared to natamycin, a conventional antifungal agent.

Safety Profile

Voriconazole eye drops have shown a generally favorable safety profile, with most adverse effects being mild and transient. Ocular irritation, burning, stinging, and blurred vision are among the most commonly reported side effects [11]. Systemic side effects associated with oral or intravenous administration of Voriconazole are rare with topical use. However, caution should be exercised when prescribing Voriconazole eye drops to patients with hepatic impairment or those taking medications that may interact with Voriconazole [12].

Comparative Studies and Guidelines

Comparative studies have indicated that Voriconazole eye drops are non-inferior or superior to other antifungal agents, such as natamycin. These findings have led to the inclusion of Voriconazole as a recommended first-line treatment for filamentous fungal keratitis in various ophthalmic guidelines and expert consensus statements [13].

Conclusions

On the basis of results available, it can be concluded that HP-β-CD based voriconazole ophthalmic formulation containing BAK and EDTA provides maximum in vitro transcorneal permeate of voriconazole through goat cornea. The transcorneal permeation of voriconazole formulation containing viscosity modifier produce less permeation of drugs as compared to formulation without viscosity modifier. Increasing the viscosity of drops by addition of viscosity modifier however reduces the permeation of voriconazole. The HP-β-CD based voriconazole ophthalmic formulation containing xanthan gum, preserved with BAK and EDTA, could provide shelf life of 2 years. The microbiological studies showed that voriconazole ophthalmic solution containing xanthan gum shows better antifungal activity as compared to voriconazole and xanthan gum alone. Despite the promising results, several questions and areas for further research remain. Optimization of dosage regimens, identification of predictive factors for treatment response, and evaluation of combination therapies are avenues that warrant exploration. Voriconazole eye drops have revolutionized the management of fungal keratitis, offering improved outcomes and expanding the therapeutic options available to ophthalmologists.

In conclusion, Voriconazole eye drops represent a significant advancement in the treatment of fungal keratitis. With their broad-spectrum antifungal activity, favorable clinical efficacy, and reasonable safety profile, Voriconazole eye drops have become an important therapeutic tool for ophthalmologists. Continued research and clinical trials are essential to further elucidate the optimal use of Voriconazole and improve patient outcomes in the management of this challenging ocular condition.

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