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Case Report

Histological Effects of Intravitreal Injection of Voriconazole and Micafungin: A Review

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Abstract

Fungal endophthalmitis is an entity with increasing incidence during the last decades. It can be a very serious and vision-threatening infection which can even threaten life. Despite the emergence of new drugs, treatment is still difficult in many cases. Intravitreal administration of antifungal agents is one of the dominant therapeutic approaches in these ocular diseases. Two of the newest antifungal representatives are voriconazole, which belongs to the azoles, and micafungin, which belongs to the echinocandins. There is limited data on the effect of voriconazole and micafungin on the retina after administration of either single or multiple intravitreal injections regarding the histological findings as well as the parameters of inflammation. Further research should be conducted in order to extract a safe conclusion regarding the adverse effects of voriconazole and micafungin in retina after intravitreal administration.

Keywords: Voriconazole, Micafungin, Intravitreal injection, Retina, Histology, TNF-a, IL-6, Electron microscopy

Fungal endophthalmitis

Fungal endophthalmitis is an entity with increasing incidence during the last decades. It can be a very serious and vision-threatening infection which can even threaten life. Various factors are suggested as key factors for the increasing incidence, such as the use of corticosteroids, which facilitates the penetration of pathogens, as well as the spread of topical antibiotics, which create an environment of lower competition between microorganisms on the surface of the eye. Other causative factors are: intraocular surgery (common complication mainly after cataract surgery), eye injuries, systemic fungal infections (mainly candidiasis and aspergillosis) and immunosuppressive entities (mainly HIV infection). Fungal infections usually affect the cornea (fungal keratitis), the vitreous (fungal endophthalmitis) and ocular tunics,

such as sclerosis (fungal panophthalmitis). The most common organisms found in fungal endophthalmitis belong to the species Candida, Aspergillus and Fusarium [1-13].

Despite the emergence of new drugs, treatment is still difficult in many cases. Intravitreal administration of antifungal agents is one of the dominant therapeutic approaches in these ocular diseases. In the past, amphotericin B (AMB) was the only antifungal agent approved for intravitreal administration. However, the retinal necrosis caused by low drug levels as well as the development of resistance to its action by many types of fungi have necessitated the use of other antifungal agents with fewer side effects and possibly higher efficacy in the treatment of fungal endophthalmitis [14].

Two of the newest antifungal representatives are voriconazole, which belongs to the azoles, and micafungin, which belongs to the echinocandins.

Voriconazole

Voriconazole is a second generation triazole which acts on the enzymes of the fungal cytochrome P450, preventing the synthesis of ergosterol in the cytoplasmic membrane, thus inhibiting fungal growth [1,15-17]. It has strong biological activity against Candida, Aspergillus, Fusarium and other filamentous fungal species [18-20]. It is metabolized in the liver (explains its hepatotoxicity), while other reported side effects are vision disorders (usually reversible), rare skin rashes and teratogenicity [1,15,17,20]. The usual routes of administration are topical, oral and intraocular.

Several investigations have been conducted regarding its mode of action, activity, bioavailability and pharmacokinetics. It has been reported, that after oral administration voriconazole's concentrations in vitreous and aqueous humor has accounted for 38% and 51% of plasma levels of the substance, respectively [21]. It has shown therapeutic efficacy against fungal keratitis and endophthalmitis after intrastromal, intracameral, intravitreal, oral, and topical administration [22-28].

In vitro studies demonstrate the superiority of voriconazole over amphotericin B against *Aspergillus* spp [29-32]. Against Fusarium species, the absolute MICs of voriconazole, natamycin and amphotericin B were similar while voriconazole has a lower relative MIC than polyenes [33]. However, the minimum inhibitory concentration of voriconazole for Fusarium was higher than that for Candida and Aspergillus [34].

Other investigators recommended voriconazole as the drug of choice for oral use in the treatment of deep keratitis, scleritis and endophthalmitis as well as the prophylaxis after penetrating keratoplasty [35]. Oral administration of voriconazole as a precaution in case of ocular injury by organic material has also been recommended [36].

Topical administration at a concentration of 1 mg / ml was effective in the treatment of keratitis from *Candida, Aspergillus, Fusarium, Scedosporium* and *Paecilomyces*, among others [37-40]. Various studies in horses have shown drug penetration even with epithelial integrity [41]. Some reports support the intracorneal use of voriconazole in cases of deep keratitis that does not respond to topical and / or oral administration. Prakash and colleagues report success in three cases of keratitis using voriconazole at a dose of 50 μg / 0.1 ml [42]. Sharma and colleagues, in a series of 13 patients, also recommend the use of intrastromal voriconazole in resistant keratitis [25]. It has also been suggested that direct injection of voriconazole into the cornea increases its concentration above the minimum inhibitory concentration (MIC) for *Fusarium* species [43].

However, there have even been reports of treatment failure with voriconazole. Giaconi and colleagues reported two cases, one of keratitis due to *Fusarium oxysporum* and another due to *Colletotrichum dematium*, that did not respond to topical drug therapy [44].

Regarding the effect of intravitreal injection of voriconazole on the retina. two experimental studies have been published. Particularly, Gao, Pennesi, and colleagues demonstrated that intravitreal administration of voriconazole to rats at an intravitreal concentration of up to 25 μg / mL did not cause electroretinographical or histological lesions (study with eosin-hematoxylin staining). At doses higher than those mentioned above, voriconazole may cause retinal necrosis. Therefore, voriconazole is considered safer to use than amphotericin B in intravitreal infusion. Also, Harrison, Glickman, and colleagues compared the intravitreal administration of amphotericin B, voriconazole, and micafungin to rabbit eyes by studying the electro-retinography and histological lesions (eosin-hematoxylin staining). They concluded that amphotericin B and micafungin are equally effective in maintaining retinal function in the first 72 hours after administration with micafungin being less toxic. On the other hand, voriconazole has a disadvantage in maintaining retinal function compared to the other two substances, requires higher concentrations and is considered more toxic than micafungin. The above protocols were applied by administering only one intravitreal injection and not multiple [6].

Micafungin

Micafungin belongs to echinocandins and acts by inhibiting the synthesis of β-(1,3)-D-glucan, which is an important structural element that maintains the integrity of the fungal cell wall. It presents fungicidal action against various species of Candida and fungistatic action against *Aspergillus* [33,45,46]. In clinical practice it is administered mainly intravenously or topically. Intravitreal administration has only been attempted in experimental protocols with laboratory animals. Its safety profile has made micafungin a very promising antifungal agent [1,2].

Micafungin has also been evaluated for its efficacy and safety in ocular fungal infections. Studies have been performed both *in vivo* (animal models) and in clinical settings (human study objects). The first studies have been performed on rabbit models.

The ocular distribution of micafungin was estimated by Suzuki and colleagues in rabbit eyes after intravenous administration. Micafungin was detected at levels above its MIC in plasma, choroid and retina, but was not detected in vitreous, suggesting the potential utility of the drug in choroidal and retinal fungal infections [47].

In the study by Trujillo et al., the topical application of micafungin in the treatment of *Aspergillus* keratitis in rabbits, was found to be well tolerated [48]. In a study by Paris et al., the efficacy of intravitreal and intravenous (IV) administration of micafungin was compared with that of intravitreal and IV administration of amphotericin B and saline (control group) in the treatment of Aspergillus keratitis [49]. It was observed reduction of the fungal load and maintenance of the range of ERG for both drugs, as well as, presence of micafungin in infected eyes for several days in the case of intravitreal administration.

In a similar study by Harrison et al., intravitreal injection of micafungin showed similar results to standard treatment with voriconazole and amphotericin B in A. Fumigatus keratitis [50]. According to Hiraoka et al., topical application of micafungin (0.1%) did not affect endothelial cell density, intraocular pressure, and lacrimal lactate dehydrogenase activity with the exception of the corneal thickness, which was significantly smaller in the micafungin group, with the thickness being restored within 24 hours after final application. Histopathological studies of the cornea did not reveal any toxicity to the cornea, enhancing further the safety and tolerability of micafungin in the eye [51].

There are, of course, several studies that have reported the evaluation of micafungin in human patients. Toshikuni and colleagues reported that co-administration of micafungin with fluconazole eye drops was proved to be more effective in treating C. *albicans* endophthalmitis than systemic fluconazole treatment in a patient with cirrhosis of the liver [52].

Endogenous endophthalmitis due to *Trichosporon* species has also been shown to be treated effectively and safely within 6 weeks with co-administration of voriconazole and micafungin in a patient with diffuse trichosporonosis [53]. The efficacy and safety of topical micafungin therapy (0.1%) were found to be similar to topical fluconazole therapy (0.2%) in the treatment of Candida keratitis [54]. Micafungin in intravenous administration to a patient suffering from C. *albicans*-induced endophthalmitis showed drug penetration into vitreous and aqueous humor. However, only in the vitreous, the concentration of micafungin was above its MIC for C. *albicans* [55].

In another study, it was observed that intravenous administration of micafungin in endogenous endophthalmitis showed low levels of the drug (less than MIC) in the aqueous humor and vitreous, which was attributed to various changes in blood-retinal barrier's integrity in the 2 studies due to differences in the severity of inflammation. This difference indicates the need for concomitant intravitreal infusion of other antifungal agents in combination with intravenous micafungin therapy. Intravenous administration of micafungin, however, resulted in concentrations higher than its MIC in the cornea, choroid, and retina, suggesting a potential therapeutic role in the treatment of fungal infections at these sites [56].

However, in a study by Mochizuki et al., a clinical failure of intravenous micafungin (200 mg / day) in the treatment of C. *tropicalis* endophthalmitis was observed [57]. This failure was in contrast to the in vitro sensitivity of C. *tropicalis* to micafungin at a MIC of 0.03 mg / mL, which was determined simultaneously. This clinical failure was attributed by the authors to the characteristic paradoxical phenomenon exhibited by echinocandins [58]. However, this hypothesis was not examined by the authors, and therefore remains a conjecture.

In a clinical case reported by Monden et al., topical and intravenous administration of micafungin was found to be effective and safe in the treatment of fungal keratitis due to *Pestalotiopsis clavispora* after prior treatment with topical voriconazole and pimaricine in recurrence of infection [59]. Micafungin in combination with voriconazole has been shown to be effective in treating fungal keratitis caused by *Beauveria bassiana* [60]. Treatment success was attributed to the synergistic effect of voriconazole and micafungin and surgical clearance. This synergistic effect has also been used in the treatment of postoperative endophthalmitis caused by *Aspergillus tubingenesis* [61]. Topical micafungin has been shown to be effective and safe in treating fungal keratitis caused by *Wickerhamomyces anomalus* [62]. as well as in treating fungal keratitis and endophthalmitis caused by various fungal species and could be considered first-line antifungal agent in the treatment of ocular fungal infections [2].

Discussion and Perspectives

There is limited data on the effect of voriconazole and micafungin on the retina after single or multiple intravitreal injections regarding the histological findings as well as the parameters of inflammation. Most studies focus either on the therapeutic capacity of the drug depending on the route of administration and the type of fungus or on its pharmacokinetics and bioavailability. The empirical application of both drugs has also been reported in many clinical cases in the form of either single or multiple intravitreal injections but in the absence of histological or ERG documentation.

It is obvious that most studies refer to the clinical features

of drug use and especially in cases where intraocular fungal infection has been induced. Most experimental protocols study the therapeutic response to different doses of antifungal agents after the induction of fungal intraocular infection. While there is lack of data regarding the histological effects of the antifungals drugs on the retina in uninfected eyes, only a study by Harrison et al. enlights the effects of intravitreal administration of voriconazole as well as micafungin in rabbits'eyes performing eosin-hematoxylin staining. However, histological lesions were observed only in the eyes in which the drug was administered in combination with fungal infection, while in the eyes where the drug was only injected no lesions were observed. Regarding the dosages, intravitreal injection of micafungin at a dose of 0.06ml containing 15μg of micafungin and injection of voriconazole at a dose of 0.06ml containing 150μg of voriconazole were performed [63].

A study by Gao et al. in rat eyes showed that intravitreal administration of voriconazole in order to achieve an intravitreal concentration of 5 to 25 μg/mL did not cause retinal lesions, while intravitreal concentration of 50 μg/mL to 500μg /ml caused small foci of retinal necrosis, with disorganization especially of the photoreceptor layer and the inner nuclear layer, as well as degeneration of the photoreceptors. In contrast, the ganglion cell layer remained intact. At an intravitreal concentration of more than 500μg/ml voriconazole caused more focal necrotic areas in the retina with more pronounced photoreceptor degeneration and disorganization of the photoreceptor layer and the inner nuclear layer. In fact, focal detachment of the retina was observed in these necrotic areas. It is noteworthy that inflammatory cells were also observed in these focal areas of the retina in the presence of choroidal congestion. Therefore, Gao and his colleagues recommend intravitreal voriconazole concentration up to 25 mg / mL as safe [5].

Regarding to micafungin, according to Paris and colleagues, intravitreal administration of micafungin at a dose of 150 μg to rabbit eyes does not cause ERG lesions [64]. However, ERG was the only method of detecting retinal damage, as no histological analysis was performed. According to Kapur, intravitreal administration of micafungin to rabbit eyes at a dose of up to 0.025mg / 0.1ml did not cause histopathological lesions or ERG lesions, suggesting this dose as a safe non-toxic starting dose with adequate antimicrobial action and therefore for future use in humans for the treatment of fungal endophthalmitis [65].

To our knowledge, there are to date no similar to our recently published study histological and immunohistochemical studies of the impact of the above drugs after intravitreal injection. Our research aimed to elucidate the histological effects of the intravitreal injection of the maximum safe dosage of voriconazole and micafungin according to available literature on retina. Our study suggests the absence of inflammation and implies that TNF-α is not involved in the mechanism of retinal damage while immunohistochemical staining for IL-6 was detected as negative for ocular injection of micafungin but as mildly positive for ocular injection of voriconazole, demonstrating its potential pro-inflammatory role in the mechanism of retinal lesion after infusion [66].

Conventional histological techniques, such as eosin-hematoxylin staining did not demonstrate retinal lesions following intravitreal administration of voriconazole and micafungin. However, to our knowledge, our study it is the first to demonstrate ultrastructural lesions in the retina following voriconazole as well as micafungin injections revealing morphological alterations of the nerve fibers, and the cytoarchitecture of ganglion and photoreceptor layers indicating a possible toxic action of the previously considered safe dosages of these antifungal drugs [66].

In conclusion, our research confirms and contributes to the existing literature as our findings are consistent with the findings of respective research protocols where the same dosages of drugs do not cause retinal damage (according to ERG and eosin-hematoxylin staining) making them safe to date but simultaneously offering a new perspective regarding the ultrastructural lesions. Histological retinal lesions after intravitreal injection of voriconazole and micafungin revealed with electron microscopy, raises the question of the safe usage of these antifungal agents in the treatment of fungal intraocular infections in the future. However, the limitations of the study open new perspectives for future investigation. The small number of laboratory animals and the absence of repeated-dosing group advice that further research should be conducted in order to extract a safe conclusion regarding the adverse effects of voriconazole and micafungin in retina after intravitreal administration [66].

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