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Intrastromal voriconazole application in the topical treatment of resistant Aspergillus fumigatus keratitis

Topikal tedaviye dirençli Aspergillus fumigatus keratitinde intrastromal vorikonazol uygulaması

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Summary

To evaluate the results of the application of intrastromal voriconazole in the topical treatment of resistant Aspergillus fumigatus. We present an interventional case report. A 50 mg/0.1 mL solution of voriconazole was injected into the corneal stromal tissue around the infiltration and put on topical voriconazole (1%) after the ulcer had failed to respond to 0.15% (1.5 mg/ml) topical amphotericin B hourly and systemic convantional amphotericin B (0.1 mg/kg) per day. Clinical outcomes were assessed at each visit. After the intervention, a faster reduction in the corneal infiltration and a dramatic therapeutic reponse was observed in the patient.

Key Words: Aspergillus fumigatus, fungal keratitis, intrastromal voriconazole.

Özet

Topikal tedaviye dirençli Aspergillus fumigatus keratiti tedavisinde intrastromal varikonazol uygulamasının sonuçlarını değerlendirmek amacıyla sunulan bu çalışma girişimsel bir olgu sunumudur. %0.15 (1.5 mg/ml) saatlik topikal amfoterisin B ve günlük sistemik klasik amfoterisin B tedavisine yanıtsızlığı takiben 50 mg/0.1 mL lik vorikonazol solüsyonu infiltrasyonetrafındaki kornea stroma dokus na enjekte edildi ve topikal vorikonazol (%1) damlatıldı. Klinik sonuçlar her vizitte değerlendirildi. Girişim sonrasında korneal infiltrasyonda daha hızlı küçülme ve hastada dramatik tedavi yanıtı gözlendi. İntrastromal vorikonazol enjeksiyonu, geleneksel tedavi yöntemlerine kötü yanıt veren derin yerleşimli inatçı fungal keratit tedavisinde güvenli ve etkili bir yol olabilir.

Anahtar Sözcükler: *Aspergillus fumigatus, fungal keratit, intrastromal vorikonazol.*

Introduction

Fungal keratitis is one of the most challenging forms of infectious keratitis to treat, and it may extend to adjacent tissues, inducing scleritis or endophthalmitis that could potentially result in loss of the eye (1,2). Most available antifungal agents are fungistatic (3). This limitation, together with the poor topical penetration of fungal agents, has prompted ophthalmologists to seek more potent antifungal agents and better routes of application. Voriconazole and other new triazoles are, at least theoretically, superior to the traditionally used antifungal agents (3,4). This study presents a patient with intractable fungal keratitis treated with an intrastromal injection of voriconazole and topical voriconazole to further elucidate the effectiveness of voriconazole for the treatment of fungal keratitis.

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Case Report

A 35-year-old man, presented to the hospital with a history of pain, redness and watering in the left eye with a 21-day duration. He had trauma history previous to the 21 days. On examination, infiltration progressed to the center of the cornea. There was a hypopyon (1.5 mm)

and stromal thinning with a clinical diagnosis of keratitis, fortified antibiotics drops (cefazolin 5% half hourly and amikacin 0.3% half hourly) and ciprofloxacin 750 mg per oral twice daily were started. Corneal scrapings were obtained and sent for microbiological investigation. Bacterial or fungal growth could not be detected. On the 10th day the infiltration progressed and descemetocele was detected in the central of cornea. The patient was treated with fortified amphotericin B lipid complex (0.15%) eye drops once each hour and systemic conventional amphotericin B (0.1 mg/kg) per day. In spite of intensive therapy, the infiltration did not regress and perforation occurred on the 17th day and partial amniotic membrane transplantation was performed.

The anterior chamber tap culture was performed under strict aseptic conditions. Aspergillus fumigatus was yielded in the anterior chamber tap culture within 72 h on both fungal media and the sheep blood agar. The MIC (expressed as microgram per milliliter) for amphotericin, fluconazole, itraconazole and ketaconazole was found to be 0.5, 256, 32 and 0.19 respectively by the epsilometer test.

Pain increased and purulent secretion developed under the contact lens on the 30th day (Figure-1) and we decided to administer an intrastromal vioriconazole injection.

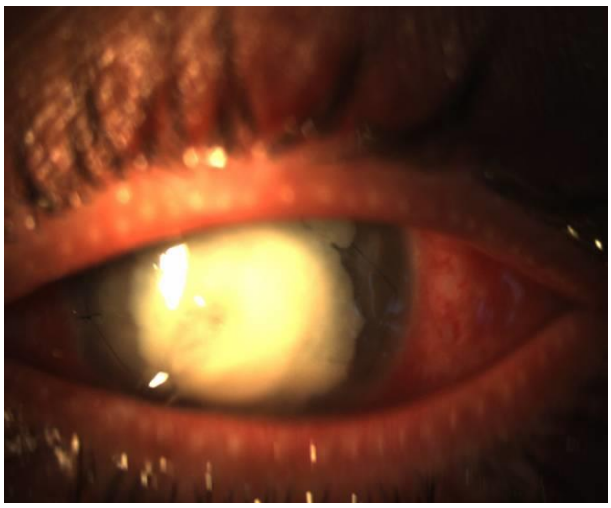

Figure-1. Corneal infiltation due to fungal infection.

An injection of voriconazole (VFEND; Pfizer Inc, USA) is available as 200 mg of white lyophilized powder in a glass vial. The powder was reconstituted with 19 ml of lactated Ringer solution (LR) to obtain 20 ml of clear concentrate containing 10 mg/ml of voriconazole. A 1-ml aliquot of this solution was further diluted with 20 ml of LR to a concentration of 0.5 mg/ml (50 µg/0.1 ml). The reconstituted solution was loaded in a 1-ml tuberculin syringe with a 30-gauge needle. After administration of peribulbar anesthesia, the patient was moved to the operating table. Under full aseptic conditions, the preloaded drug was administered under an operating microscope. A circumferential injection was made around the infiltrate (Figure-2).

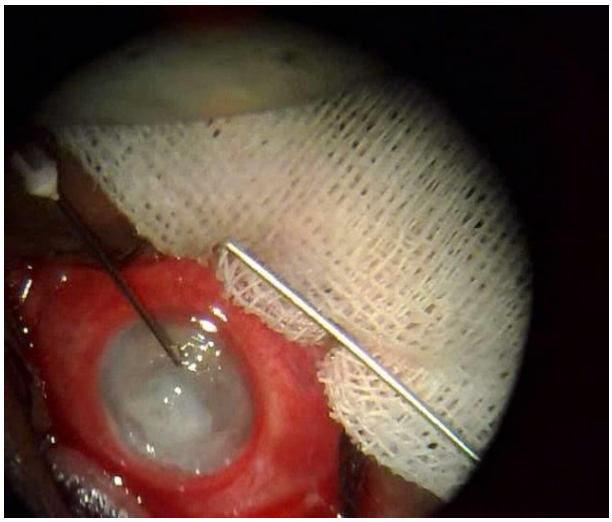

Figure-2. Intrastromal voriconazole injection.

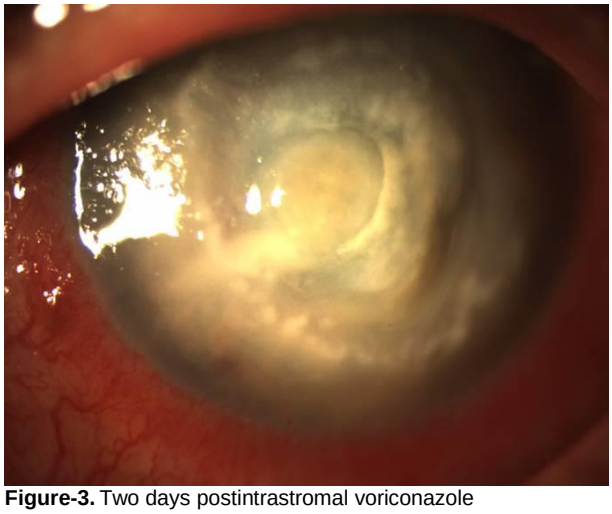

Figure-3. Two days postintrastromal voriconazole injection.

The total amount of drug injected intrastromally was 0.05 ml. After the intrastromal injection, the patient was continued on prescribed topical voriconazole (1%). Hypoyion regressed and pain decreased after two days of injection (Figure-3).

The intrastromal voriconazole injection was repeated due to partial response after two weeks. The patients was continued on a topical antifungal therapy for one week after the complete resolution of infection. He had a vascularized scar in the center of the cornea with no inflammation after the second injection (Figure-4).

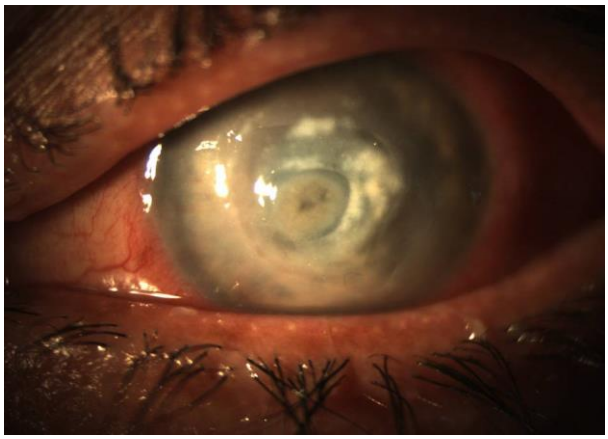

Figure-4. Healed corneal infiltration after second intrastromal injection.

Discussion

Fungal keratitis accounts for nearly 50% of all cases of infectious keratitis in developing countries and has a poor prognosis compared with bacterial keratitis (1-4). Currently available topical antifungal drugs have limitations such as poor penetration into the eye, limited spectrum of activity and surface toxicity (3-5). In this study, the result of using intrastromal voriconazole in a *Aspergillus fumigatus* keratitis non-responsive to topical and systemic conventional amphotericin B therapy is reported.

Voriconazole has an excellent broad spectrum of anti-fungal activity and is active against species that are known to be resistant to the other antifungal agents commonly used in fungal keratitis. Several fungal keratitis cases have been reported regarding topical and systemic voriconazole treatment (3-7). Prakash et al. (5) reported a favorable outcome using intrastromal voriconazole injection in 3 patients with deep recalcitrant fungal keratitis. In each of the three patients smears were positive for fungus and on cultures, *Fusarium* species was identified in two eyes and *Aspergillus* species in one eye . In one patient, there was minimal intrastromal bleeding in the inferior part of the cornea but this was resolved in seven days. Systemic voriconazole 200 mg twice a day was additionally given to one patient because of scleral involvement. The infection resolved completely in all three eyes after the intrastromal injection of voriconazole.

Sharma et al. reported on twelve patients of smear and/or culture positive fungal keratitis not responding to topical and systemic antifungal therapy who were treated with additional intrastromal voriconazole therapy (6). Organisms isolated were *Aspergillus* species (n=8), *Fusarium* species (n=3) and *Curvularia* (n=1). Patients were given one or more intrastromal injection of voriconazole (50 µg in 0.1 ml) at the junction of clear cornea and infiltrates. All patients continued to receive topical and systemic antifungal therapy. Of the 12 eyes, 10 eyes healed with scar formation. Two corneas perforated and required therapeutic penetrating keratoplasty. The best-corrected visual acuity was less than 20/1200 in all patients at the time of presentation, which improved to better than 20/400 in 10 eyes and 20/40 in eyes that underwent penetrating keratoplasty at the end of 24.75±2.14 weeks' follow-up. Reduction of the corneal infiltration size after intrastromal injection of voriconazole suggests drug toxicity and sterile keratolysis as contributing factors, accompanied by an infectious process may be leading to microperforation of the cornea. In our case we did not observe any toxic effect with the drug after the injection.

Stiatri et al. (7) presented 3 patients with recalcitrant fungal keratitis treated with 50 mg/0.1 mL intrastromal voriconazole injection and a (%1) topical voriconazole application after the ulcer failed to respond to 5% topical natamycin and oral ketoconazole. A dramatic therapeutic response was observed in 2 patients. An amniotic membrane transplantation was required to seal the microperforation in one patient with a chemical burn superinfected with Fusarium. However, they stated that intrastromal injection of voriconazole may be used as a modality of treatment for managing cases of recalcitrant fungal keratitis.

Nowadays ophtalmologists have acquired experience with intrastromal voriconazole injection. In this paper, only one patient with fungal keratitis which was treated with intrastromal voriconazole injection was presented but the result was successful. We can conclude that judicious and timely use of intrastromal voriconazole injection as an adjunctive therapy may be undertaken in selected patients who are unresponsive to other forms of antifungal therapy.

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