Topical Ketoconazole for Fungal Keratitis

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Six patients (five men and one woman, 19 to 57 years old) with laboratory-proven fungal corneal infections were successfully treated with topical ketoconazole, a synthetic imidazole derivative. No signs of progression of the corneal infection were seen after the antifungal therapy was initiated. The clinical signs of corneal infection disappeared after three (Aspergillus infections) to seven weeks (Fusarium infections) of ketoconazole therapy. In all cases, posttreatment visual acuities were better than pretreatment visual acuities. No significant biomicroscopic signs of ocular surface toxicity were noted.

Ketoconazole is a relatively new water-soluble synthetic imidazole antimycotic agent with a broad spectrum of activity. It is absorbed into the blood after oral administration and it is safe and effective against human superficial and deep mycosis. In animal experiments, this drug was well tolerated topically and it penetrated the eye well. After topical administration to human volunteers it produced no biomicroscopic signs of ocular surface toxicity (M. A. Torres, H. Cavazos-Adame, and G. Velasco-Gallegos, unpublished data). In rabbits it demonstrated both prophylactic potential and therapeutic efficacy in fungal keratitis. Two cases of human keratomycosis were successfully treated with oral ketoconazole. We recently used topical ketoconazole to treat six cases of human mycotic keratitis.

Subjects and Methods

All six patients thought to have fungal corneal infection had corneal scrapings performed on the day of admission (Table 1). The scrapings were performed under the slit-lamp biomicroscope. Stromal fragments, scraped from the base and margins of the ulcer, were smeared on glass slides for Gram and Giemsa staining. The specimens were also inoculated at 35°C on blood agar, chocolate agar, eosin-methylene blue agar, Sabouraud's dextrose agar, and thioglycolate medium and at 20°C in blood agar and Sabouraud's dextrose agar.

Our criteria for diagnosis of keratomycosis included biomicroscopic findings compatible with corneal fungal infection, microscopic observation of hyphal fragments on stained smears of the corneal scrapings, and fungal growth in the C-streaks on at least two culture plates inoculated with scraped material from the lesion. All the patients included in our study were treated with topical ketoconazole 2% and atropine 1% eyedrops.

To prepare the antifungal medication, we reduced a 200-mg commercially available ketoconazole tablet to a fine powder by manual triturating. A suspension was obtained by dispersing the powdered drug in 5 ml of 4.5% sterile boric acid solution. We added 5 ml of hydroxypropylmethylcellulose to increase the viscosity of the suspension. To make the doses uniform, the dropper-bottle was vigorously shaken before instillation of the drug into the eye.

We have selected three representative case histories for more detailed discussion.

Case Reports

Case 2

A 56-year-old man was struck in his left eye by a tree branch on Oct. 24, 1983. A few hours later, the eye became red, painful, and photophobic. Topical tetracycline ointment did not improve his symptoms.

Three days later, the patient was first examined in our outpatient clinic. Uncorrected visual acuity in the affected eye was counting fingers at 4 feet. A slit-lamp examination of the...
TABLE 1
CLINICAL CHARACTERISTICS OF PATIENTS WITH FUNGAL KERATITIS AT INITIAL EXAMINATION

<table>
<thead>
<tr>
<th>PATIENT NO., SEX, AGE (YRS)</th>
<th>PREDISPOSING OCULAR CONDITION</th>
<th>PREVIOUS TOPICAL MEDICATION</th>
<th>INITIAL VISUAL ACUITY</th>
<th>CHARACTERISTICS OF THE LESION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, M, 49</td>
<td>None</td>
<td>Chloramphenicol eyedrops</td>
<td>20/200</td>
<td>Paracentral superficial ulcer with underlying dense infiltrate (3.5 mm in diameter; 30% of corneal thickness in depth)</td>
</tr>
<tr>
<td>2, M, 56</td>
<td>Corneal foreign body of vegetable origin</td>
<td>Tetracycline ointment</td>
<td>C.F. at 4 ft*</td>
<td>Central superficial ulcer with underlying C-shaped dense infiltrate (4 mm in diameter; 60% of corneal thickness in depth)</td>
</tr>
<tr>
<td>3, M, 42</td>
<td>Corneal abrasion with vegetable matter</td>
<td>Chloramphenicol eyedrops</td>
<td>20/200</td>
<td>Central superficial ulcer with faint stromal infiltrate with projections (3.5 mm in diameter; 20% of corneal thickness in depth)</td>
</tr>
<tr>
<td>4, M, 30</td>
<td>None</td>
<td>Dexamethasone eyedrops</td>
<td>C.F. at 12 ft*</td>
<td>Central superficial ulceration with dense stromal infiltrate (5 mm in diameter; 60% of corneal thickness in depth)</td>
</tr>
<tr>
<td>5, F, 19</td>
<td>None</td>
<td>Dexamethasone eyedrops</td>
<td>C.F. at 4 ft*</td>
<td>Paracentral superficial ulcer with underlying dense infiltrate with feathery edges and a pseudopodal extension (4.5 mm in diameter; 60% of corneal thickness in depth)</td>
</tr>
<tr>
<td>6, M, 57</td>
<td>Corneal foreign body of vegetable origin</td>
<td>Dexamethasone eyedrops</td>
<td>C.F. at 12 ft*</td>
<td>Central infiltrate with feathery edges surrounding a thorn fragment embedded in the anterior two thirds of the corneal stroma</td>
</tr>
</tbody>
</table>

*C.F., counting fingers.

left cornea showed a 3.5-mm superficial ulceration with a 4-mm C-shaped stromal infiltrate involving the anterior two thirds of the cornea (Fig. 1, top left). A small thorn fragment was removed from the center of the lesion and cultured in Sabouraud’s dextrose agar. Gram- and Giemsa-stained corneal scrapings failed to demonstrate any micro-organisms. Fortified gentamicin and cefazolin eyedrops were administered every 15 minutes but the corneal infiltrate continued to progress during the next 26 hours. At that time, a small fungal colony was seen growing over the cultured foreign body. Repeat corneal scrapings done at this time demonstrated abundant hyphal forms (Fig. 1, top right). The fungal colony growing on the cultured foreign body was identified as *Aspergillus flavus*. The same organism was later recovered from several media inoculated during the first and second corneal scrapings. Fortified antibiotic eyedrops were discontinued and topical ketoconazole 2% was administered every 30 minutes (Table 2). After 17 days of therapy, the lesion had healed completely, leaving a 3-mm stromal scar and an uncorrected visual acuity of 20/40 in the left eye.

Case 3
A 42-year-old man was struck in his left eye by a wood splinter on Dec. 11, 1983. The injury caused immediate blurring of vision, redness, and foreign-body sensation. Topical chloramphenicol eyedrops did not improve his symptoms.
Case 2

A 19-year-old woman first noted redness and mild foreign-body sensation in her left eye on March 8, 1984. Her physician prescribed topical dexamethasone eyedrops but her symptoms gradually increased until severe pain and photophobia developed. The patient was referred here for evaluation and treatment of a corneal lesion on March 12, 1984.

On admission, uncorrected visual acuity in the affected eye was counting fingers at 4 feet. A slit-lamp examination of the left cornea disclosed a 2.5-mm superficial ulceration with a 4.5-mm white dense infiltrate with feathery margins involving the anterior two thirds of the corneal stroma (Fig. 3, top left). Gram- and Giemsa-stained corneal scrapings showed abundant hyphal fragments (Fig. 3, top right). Treatment with topical ketoconazole 2% every 30 minutes and mydriatic-cycloplegic eyedrops twice daily was initiated (Table 2). Three days after the corneal scrapings were cultured, *Fusarium solani* was growing on blood agar, chocolate agar, and Sabouraud’s dextrose agar.

The patient was referred here for evaluation and treatment of a corneal lesion on Dec. 20. Uncorrected visual acuity in the affected eye was 20/200. A slit-lamp examination of the left cornea disclosed a 2.5-mm superficial ulceration with a 3.5-mm feathery white stromal infiltrate 20% of the corneal thickness in depth (Fig. 2, top left). Gram- and Giemsa-stained corneal scrapings showed abundant hyphal forms (Fig. 2, top right). Treatment with topical ketoconazole 2% every 30 minutes and atropine 1% twice daily was initiated (Table 2). Two days after the corneal scrapings were cultured, several colonies of *Alternaria* sp. were growing on blood agar and Sabouraud’s dextrose agar (Fig. 2, bottom left). The corneal epithelium partially covered the ulcer and the stromal infiltrate was less dense after five days of treatment. On Jan. 18, 1984, topical ketoconazole was discontinued. The left eye showed no signs of inflammatory reaction the the corneal lesion had healed completely (Fig. 2, bottom right). The patient was left with a 3-mm corneal scar and an uncorrected visual acuity of 20/60.
TABLE 2
LABORATORY FINDINGS, TREATMENT, AND RESULTS

<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>ORGANISM</th>
<th>TREATMENT</th>
<th>FINAL APPEARANCE OF CORNEA</th>
<th>FINAL UNCORRECTED VISUAL ACUITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aspergillus fumigatus</td>
<td>Topical ketoconazole 2%: 1 drop every 30 mins during waking hours and 1 drop/hr at night for 15 days; then 1 drop every waking hour for 5 days</td>
<td>3-mm paracentral corneal scar; healed ulcer with smooth corneal surface</td>
<td>20/60</td>
</tr>
<tr>
<td>2</td>
<td>Aspergillus flavus</td>
<td>Topical gentamicin (14 mg/ml) and cefazolin (50 mg/ml): 1 drop every 15 mins for 36 hrs; then topical ketoconazole 2%: 1 drop every 30 mins during waking hours and 1 drop/hr at night for 10 days; then 1 drop every waking hour for 7 days</td>
<td>3-mm central stromal haze: healed ulcer with smooth corneal surface</td>
<td>20/40</td>
</tr>
<tr>
<td>3</td>
<td>Alternaria sp.</td>
<td>Topical ketoconazole 2%: 1 drop every 30 mins during waking hours and 1 drop/hr at night for 20 days; then 1 drop every waking hour for 10 days</td>
<td>3-mm central stromal scar: healed ulcer with smooth corneal surface</td>
<td>20/60</td>
</tr>
<tr>
<td>4</td>
<td>Fusarium solani</td>
<td>Topical ketoconazole 2%: 1 drop every 30 mins during waking hours and 1 drop/hr at night for 30 days; then 1 drop every waking hour for 18 days</td>
<td>4-mm central stromal scar: healed ulcer with smooth corneal surface</td>
<td>20/80</td>
</tr>
<tr>
<td>5</td>
<td>Fusarium solani</td>
<td>Topical ketoconazole 2%: 1 drop every 30 mins during waking hours and 1 drop/hr at night for 35 days; then 1 drop every waking hour for 15 days</td>
<td>4.5-mm central stromal scar: healed ulcer with smooth corneal surface</td>
<td>C.F. at 8 ft*</td>
</tr>
<tr>
<td>6</td>
<td>Mycelia sterilia</td>
<td>Topical ketoconazole 2%: 1 drop every 30 mins during waking hours and 1 drop/hr at night for 20 days; then 1 drop every waking hour for 5 days</td>
<td>3-mm central stromal scar: healed ulcer with irregular corneal surface</td>
<td>20/120</td>
</tr>
</tbody>
</table>

*C.F.: counting fingers.

During the first two weeks of therapy, the infiltrate and ulceration remained unchanged except for subtle variations at the edges of the lesion. The cornea began to improve during the third week of treatment and by the seventh week the infiltrate had vanished and the ulcer had healed. Topical ketoconazole was discontinued 50 days after initiation of therapy. The patient was left with a 4.5-mm central corneal scar (Fig. 3, bottom left) and an uncorrected visual acuity of counting fingers at 8 feet.

Results

In none of the six cases were there signs of progression of the corneal infection after ketoconazole therapy was initiated. In Cases 1 and 2, the eye showed signs of improvement as little as 72 hours after initiation of the treatment. The first signs of resolution in Cases 3 and 6 were noted after five days of therapy. Cases 4 and 5 responded slowly. In these pa-
Fig. 2 (Torres and associates). Case 3, left eye. Top left. At the initial examination, the central cornea had a 3.5-mm infiltrate with marginal projections. Top right. Septate hyphal fragments in the corneal stroma (Giesma stain, ×400). Bottom left, Alternaria sp. cultured from the corneal stroma showing chains of muriform conidia. Bottom right. Only a faint corneal scar remained at the site of the fungal lesion after 30 days of topical ketoconazole therapy.

Fig. 3 (Torres and associates). Case 5, left eye. Top left. At the initial examination, the lower cornea had a 4.5-mm dense infiltrate with feathery margins and a pseudopodal extension (arrows) Top right. Abundant hyphal fragments in the smear from the corneal lesion (Gram stain, ×400). Bottom left. After seven weeks of therapy, only a corneal nebula remained at the site of the lesion.
tients, the cornea remained unchanged during the first two weeks of treatment. Complete resolution of the corneal infection was achieved in all cases after three to seven weeks of therapy. The corneal lesions resolved, leaving opacified scars. Posttreatment visual acuities were better than initial visual acuities. Topical ketoconazole was well tolerated and produced no significant biomicroscopic evidence of ocular surface toxicity.

**Discussion**

Imidazole derivatives have been used successfully in the treatment of fungal corneal infections. Ketoconazole is a newer imidazole agent inhibitory in vitro to a wide range of pathogenic yeasts and fungi. In laboratory determinations of minimal inhibitory concentrations, ketoconazole compares unfavorably with other imidazole derivatives. This poor performance in vitro contrasts sharply with its excellent performance in animal models of fungal disease and its therapeutic effectiveness in human mycotic infections.

Our six patients were cured with topical ketoconazole alone. Except for atropine 1%, all other medications were discontinued after the identification of hyphal fragments on the stained corneal scrapings.

Ketoconazole was effective in two patients (Cases 4 and 5) with *Fusarium* infections, a fungus known to be highly resistant in vitro to the imidazole agents. However, it should be noted that the rate of improvement in these cases was initially disappointing and therapy had to be maintained for seven weeks until resolution of the infection was achieved.

The ketoconazole 2% suspension was well tolerated by the conjunctival and corneal epithelium. Drug deposits were seen on the palpebral margin, the inferior fornix, and adherent to the ulcer surface. Possibly this prolonged retention increases the drug's effect.

**References**