MICONAZOLE THERAPY FOR KERATOMYCOSIS

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I treated seven patients with keratomycosis (four with Candida infections and three with Aspergillus infections) with topical and subconjunctival miconazole. Progressive corneal ulceration stopped in each case, and clinical evidence of corneal infection disappeared. Posttreatment visual acuities were at least as good as (and usually better than) pretreatment visual acuities. Superficial punctate keratitis was associated with prolonged (one to two weeks) hourly instillation of miconazole, but there was no evidence of serious ocular toxicity.

During the past 30 years, fungal infections have been increasingly reported as a cause of keratitis. The less-than-optimal resolution of such cases has been attributed to delayed diagnosis and to the lack of safe, effective antifungal agents that adequately penetrate ocular structures. In 1975, pimaricin (Natamycin), a broad-spectrum antifungal agent with low toxicity, became the first antifungal agent approved for ocular use in the United States. It is effective for superficial corneal ulcers caused by fungi sensitive to it, but, because it does not penetrate the cornea or sclera well, it is not effective against deeper corneal ulcers. Amphoterin B does not penetrate well either, and is extremely toxic. Flucytosine is well tolerated, but has a limited antifungal range.

Miconazole is a broad-spectrum antifungal agent that has already proven to be safe and effective in human keratomycosis. In animal experiments, this drug was well tolerated topically and subconjunctivally, and it penetrated the ocular coats readily. I recently used miconazole to treat seven cases of keratomycosis in humans.

SUBJECTS AND METHODS

The seven patients were found to have keratomycosis after being referred here. Table 1 shows their clinical characteristics at my initial examination. Scrapings from the edges and deep base of each corneal ulcer were obtained for Gram and Giemsa staining. They were also used for culture at 35 C on Sabouraud’s medium and in cooked meat broth, and at 20 C on blood agar. I used the following criteria for diagnosis of fungal keratitis: (1) clinical features compatible with fungal keratitis; (2) fungal elements seen on stained smears of the corneal scrapings; and (3) growth of fungal organisms in the “C streaks” on at least two culture plates with scrapings from the involved cornea. Antifungal sensitivities were determined with tube and plate dilution methods. All patients were then treated in the hospital with 0.3% topical...
<table>
<thead>
<tr>
<th>Case, Sex, Age (yrs)</th>
<th>Systemic Disease</th>
<th>Corneal Status Before Keratomycosis</th>
<th>Ocular Drug Use</th>
<th>Visual Acuity of Affected Eye</th>
<th>Ulcer Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, M, 36</td>
<td>None</td>
<td>L.E.: Exposure keratitis secondary to traumatic palsy of 7th cranial nerve (4 yrs)</td>
<td>Dexamethasone, chronic use</td>
<td>6/12 (20/40)</td>
<td>Peripheral ulcer, 2 × 3 mm; anterior 25% of stroma lost; dense white stromal infiltrate with feathery borders; endothelial plaque; small hypopyon.</td>
</tr>
<tr>
<td>2, F, 63</td>
<td>None</td>
<td>Normal</td>
<td>None</td>
<td>C.F. at 2 ft*</td>
<td>Large central ulcer with many dense white stromal infiltrates; endothelial plaque; small hypopyon.</td>
</tr>
<tr>
<td>3, F, 67</td>
<td>None</td>
<td>Normal</td>
<td>None</td>
<td>6/6 (20/20)</td>
<td>Peripheral ulcer with surrounding and underlying dense white infiltrate.</td>
</tr>
<tr>
<td>4, M, 45</td>
<td>None</td>
<td>Corneal transplant for aphakic bullous keratopathy (1 mo previously)</td>
<td>Dexamethasone and gentamicin</td>
<td>6/60 (20/200)</td>
<td>Paracentral superficial ulcer with underlying and surrounding dense white stromal infiltrate; two satellite superficial infiltrates.</td>
</tr>
<tr>
<td>5, F, 44</td>
<td>Chronic mucocutaneous candidiasis</td>
<td>Bilateral recurrent corneal ulcers (10 yrs)</td>
<td>Artificial tears</td>
<td>H.M.*</td>
<td>Inferior, paracentral descemetocele, 4 × 3 mm; 2 fluffy white infiltrates on Descemet's membrane; diffuse stromal infiltrate extending from edges of descemetocele.</td>
</tr>
<tr>
<td>6, M, 43</td>
<td>Diabetic acidosis</td>
<td>No history of corneal disease</td>
<td>None</td>
<td>6/60 (20/200)</td>
<td>Central epithelial defect 6 mm in diameter with faint anterior stromal haze.</td>
</tr>
<tr>
<td>7, F, 38</td>
<td>None</td>
<td>Normal</td>
<td>None</td>
<td>6/60 (20/200)</td>
<td>Central corneal ulcer (3 mm in diameter; 25% of corneal thickness in depth) with fluffy white infiltrate in underlying and surrounding stroma; 2 satellite stromal lesions; endothelial plaque; small hypopyon.</td>
</tr>
</tbody>
</table>

*C.F., counting fingers; H.M., hand motions.*
**TABLE 2**  
TREATMENT AND RESULTS

<table>
<thead>
<tr>
<th>Case</th>
<th>Organism</th>
<th>Sensitivity of Organism (µg/ml)</th>
<th>Treatment*†</th>
<th>Anatomic Result</th>
<th>Final Visual Acuity in Affected Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aspergillus fumigatus</td>
<td>0.2 0.7 0.4</td>
<td>Miconazole (1 drop/hr for 5 days; then 1 drop/waking hr for 2 wks; then 1 drop 6 times/day for 3 wks)</td>
<td>Healed ulcer with peripheral corneal stromal thinning and scarring.</td>
<td>6/12 (20/40)</td>
</tr>
<tr>
<td>2</td>
<td>Aspergillus flavus</td>
<td>0.4 &gt;100 20.0</td>
<td>Miconazole (subconjunctival, 10 mg/day for 5 days; 1 drop/hr for 5 days; then 1 drop/waking hr for 4 wks; then 1 drop 6 times/day for 7 wks)</td>
<td>Healed ulcer with clearing of stromal infiltrates and hypopyon; corneal scar.</td>
<td>C.F. at 2 ft*</td>
</tr>
<tr>
<td>3</td>
<td>Aspergillus fumigatus</td>
<td>0.4 0.8 40.0</td>
<td>Miconazole (subconjunctival, 10 mg/day for 3 days; 1 drop/hr for 5 days; then 1 drop/waking hr for 2 wks; then 1 drop 6 times/day for 3 wks)</td>
<td>Healed ulcer with clearing of stromal infiltrate; small peripheral anterior stromal scar.</td>
<td>6/6 (20/20)</td>
</tr>
<tr>
<td>4</td>
<td>Candida albicans</td>
<td>0.2 0.8 0.4</td>
<td>Miconazole (subconjunctival, 10 mg once; 1 drop/hr for 4 days; then 1 drop/waking hr for 3 wks; then 1 drop 6 times/day for 4 wks)</td>
<td>Healed ulcer with paracentral stromal scar.</td>
<td>6/18 (20/60)</td>
</tr>
<tr>
<td>5</td>
<td>Candida albicans  Staphylococcus aureus  Proteus mirabilis</td>
<td>Sensitive to cefazolin and gentamicin  Sensitive to cefazolin and gentamicin</td>
<td>Miconazole (subconjunctival, 10 mg/day for 4 days; 1 drop/hr for 10 days; then 1 drop/waking hr for 4 wks; then 1 drop 6 times/day for 4 wks); gentamicin (subconjunctival, 40 mg/day for 4 days; 1 drop/hr for 10 days; then 4 times/day for 2 wks);</td>
<td>Clear lamellar graft; white infiltrates at host-graft interface disappeared; chronic Candida infection cleared up.</td>
<td>6/60 (20/200)</td>
</tr>
<tr>
<td>6</td>
<td>Candida albicans</td>
<td>0.8 0.1 0.4</td>
<td>Miconazole (subconjunctival, 133 mg/day for 4 days; 1 drop/hr for 10 days; then 4 times/day for 2 wks); Ketoconazole (oral, 200 mg/day beginning 14 days after surgery)</td>
<td>Healed ulcer; mild anterior paracentral stromal haze.</td>
<td>6/24 (20/80)</td>
</tr>
<tr>
<td>7</td>
<td>Candida albicans</td>
<td>0.4 0.4 0.2</td>
<td>Miconazole (subconjunctival, 10 mg/day for 5 days; 1 drop/hr for 5 days; then 1 drop/waking hr for 4 wks; then 1 drop 6 times/day for 4 wks)</td>
<td>Healed ulcer; stromal scar</td>
<td>6/15 (20/50)</td>
</tr>
</tbody>
</table>

*All patients also received 4% atropine. All except Patient 5 also received 0.3% topical gentamicin 4 times per day for broad-spectrum antibacterial protection because of ulcerating devitalized tissue.

†Concentrations of the topically administered drugs were as follows: miconazole (in the form of the intravenous preparation Monistat), 10 mg/ml; gentamicin, 14 mg/ml; and cefazolin, 133 mg/ml.

*C.F., counting fingers.
gentamicin, 4% atropine, topical miconazole (10 mg/ml), and subconjunctival miconazole (10 mg).

I have selected three of the seven cases for discussion. The treatment and results for all seven cases are summarized in Table 2.

**Case reports**

**Case 2**—A 63-year-old woman was referred here for evaluation and treatment of a corneal ulcer. The ulcer had been treated at another hospital for 18 days with gentamicin (administered topically every hour and subconjunctivally once each day) and bacitracin (administered topically every hour). Several scrapings and cultures at the referring hospital failed to isolate any organisms. Five days before the patient was admitted to the referring hospital, her right eye had become red and painful. She treated the eye with teabag compresses. Visual acuity at my first examination of the patient was R.E.: counting fingers at 2 ft and L.E.: 6/12 (20/40). The right cornea was studded with numerous stromal infiltrates. A large endothelial plaque and a small hypopyon with hyphema were present (Fig. 1, left). Corneal scrapings showed hyphal forms. Three days after the corneal scrapings were cultured, *Aspergillus flavus* was growing on the blood agar.

Therapy with topical and subconjunctival miconazole was begun (Table 2). Over the next 12 weeks, the corneal infiltrates and hypopyon vanished. The patient was left with a scarred cornea and visual acuity of counting fingers at 3 ft in her right eye (Fig. 1, right).

**Case 5**—A 44-year-old woman was admitted here for treatment of a descemetocele in her left eye. Chronic mucocutaneous candidiasis had been diagnosed in this patient when she was 6 years old; she had developed idiopathic thrombocytopenic purpura at the age of 16 years. The subsequent appearance of arthritis and positive serologic findings resulted in the diagnosis of systemic lupus erythematosus. Her ten-year history of ocular involvement in candidiasis was marked by episodes of bilateral corneal ulcers and progressive corneal vascularization. The predominant form of antifungal therapy had been intravenous and topical amphotericin B and oral clotrimazole.

At my first examination of this patient, her visual acuity was hand motions in both eyes. The conjunctiva of each eye was injected, and the inferior fornix foreshortened. Extensive corneal scarring and vascularization were present in the right eye; there was a wedge-shaped superficial white plaque (Fig. 2, left). In the left eye there was a horizontally oriented inferior descemetocele, with two fluffy, white infiltrates on Descemet's membrane (Fig. 3, top left and top right). Corneal scrapings of the edges of the ulcer yielded gram-positive cocci, gram-negative rods, and yeast forms. Therapy was begun with topical and subconjunctival gentamicin, cefazolin, and miconazole (Table 2). The topical medications were instilled hourly, 15 minutes apart.

Two days after she was admitted to the hospital, the patient underwent lamellar keratoplasty carried down to Descemet's membrane in her left eye. The white infiltrates on Descemet's membrane were still present after the operation. Cultures of the infiltrates obtained during surgery grew *Candida* organisms. The infiltrates vanished during the 14 days of postoperative therapy (Fig. 3, bottom left). Systemic ketoconazole therapy (200 mg/day, taken orally) was then begun; during the next four weeks the patient's topical medication was gradually reduced and discontinued. The patient has continued to take systemic ketoconazole for six months, and has been free of *Candida* infections during that time. Visual acuity is now 6/60 (20/200) in both eyes. The right eye has improved: the white plaque has disappeared, and the corneal vessels have emptied (Fig. 2, right).

**Case 6**—A 43-year-old man was admitted here while in a state of diabetic acidosis. At the time of admission, the medical team noted conjunctival edema and injection of the right eye and candidal intertrigo and sought an ophthalmologic consultation. There was a central epithelial defect in the right eye. When the patient first regained consciousness, his visual acuity was 6/60 (20/200) in the right eye. A faint anterior stromal haze was present in the area of the epithelial defect. Candidal keratitis was suspected. Corneal scrapings confirmed this diagnosis; budding yeast forms and pseudohyphae were seen on smear, and *Candida albicans* grew on blood agar at room temperature. Therapy with subconjunctival and topical miconazole continued for the next nine weeks (Table 2). The corneal ulcer resolved, leaving a paracentral corneal stromal scar and a visual acuity of 6/24 (20/80) in the right eye.

**Results**

In five of the seven patients, there was evidence of deep corneal foci of fungal invasion. In each case, after four to six weeks of miconazole therapy progressive corneal ulceration stopped and clinical evidence of corneal infection disappeared. In Case 5, I used lamellar keratoplasty as well as antifungal therapy with miconazole and ketoconazole. Topical miconazole therapy was routinely continued for six to 12 weeks. Ocular integrity was preserved in each instance; corneal scarring was left after the infections were resolved. Posttreatment visual acuities were at least as good as (and usually better than) pretreatment visual acuities (Tables 1 and 2). There was no significant
clinical evidence of ocular toxicity of miconazole, although hourly instillation of the drug appeared to contribute to superficial punctate keratitis. These changes resolved when the frequency of instillation of all ocular drugs was reduced. Subconjunctival miconazole (10 mg/day for up to five days) was well tolerated.

**DISCUSSION**

In treating patients with corneal fungal infections, ophthalmologists are confronted with three major difficulties: the limited selection of antifungal agents available, the poor intraocular penetration of many of the available agents, and the toxicity of these agents. The need for safe, effective antifungal agents with broad ranges and good ocular penetration has been expressed many times since Leber\(^7\) first described keratomycosis. Jones\(^1\) emphasized the disastrous outcome of many cases of keratomycosis. He also stressed the poor ocular penetration and unacceptable toxicity of amphotericin B and the poor penetration of pimaricin. His early clinical experience with imidazole antifungal agents, including miconazole, suggested that these drugs have the characteristics necessary for use as ocular antifungal agents: high antifun-
gal activity, a broad range, the ability to penetrate the ocular coats, and nontoxicity. Other studies defined more precisely the ocular penetration and toxicity of miconazole. This report confirmed Jones's findings on the clinical efficacy of miconazole for keratomycosis caused by Candida and Aspergillus organisms. Miconazole, whether administered topically, subconjunctivally, or both, appears to be an alternate method of treating keratomycosis.

In Case 5, the role ketoconazole played in the outcome in the left eye and in the improvement in the right eye is unclear. In vivo data in animals suggest that orally administered ketoconazole penetrates the cornea extremely well. For this reason (as well as my confidence in miconazole penetration into the cornea and aqueous humor after topical and subconjunctival administration), I believed lamellar keratoplasty was the most reasonable choice of surgical procedures for this patient. Lamellar keratoplasty is, in general, ill-advised in keratomycosis, because fungi remaining in the host tissue may proliferate and produce progressive fungal keratitis postoperatively. I was concerned about postoperative wound healing because of the extreme bilateral pathologic changes of the ocular surface and the conjunctival cicatrization in Case 5. I believed that lamellar grafting was safer than penetrating keratoplasty in this circumstance and that any remaining fungi could be eradicated by topical and subconjunctival miconazole and orally administered ketoconazole.

The significance of the white plaque in the right cornea of this patient is unclear. Cultures of the ocular surface epithelium...
(cornea and conjunctiva) of the right eye were positive for *C. albicans*. This eye did not receive topical antifungal therapy; surface cultures done after six weeks of oral ketoconazole therapy were negative.

**References**


*Fifty years ago this month* in The Journal

The scientific proceedings of the Amsterdam Congress of 1929 give concrete expression to the truth that all parts of the world can furnish observations which throw new light on our problems and furnish new inspiration and new methods for their solution. Different nations, like different individuals, may see things differently; and, reporting what they see, may bring individual contributions of high value to our swiftly developing stock of common knowledge. In Switzerland Gonin, influenced by the views of Leber of Heidelberg, and corroborated by those who first learned of his new treatment for detached retina, has almost reversed the prognosis and attitude of ophthalmologists toward that condition.

Jackson, E.: *World Ophthalmology*  