Therapeutic Failures with Miconazole

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A retrospective review of therapeutic failures of miconazole in three patients is presented. Miconazole, a new imidazole derivative, is a broad-spectrum antifungal agent purportedly effective topically, orally, and parenterally against a number of species of fungi. Three patients with the following culturally proven deep fungal infections were treated with miconazole: (i) destructive arthritis (Sporothrix schenckii), (ii) meningoencephalitis (Cryptococcus neoformans), and (iii) disseminated aspergillosis (Aspergillus fumigatus). All the organisms were susceptible in vitro to 1.56 µg or less of miconazole per ml using a broth dilution technique. In each patient, miconazole administered intravenously in dosages of 30 mg/kg per day failed to control or eradicate infection. Miconazole serum levels ranged from <0.5 to 4.35 µg/ml as determined by radial diffusion bioassay. Cerebrospinal fluid levels were virtually undetectable. In one patient (C. neoformans), miconazole was given intraventricularly in doses of 15 mg without response. Therapeutic failures were attributed to suboptimal body fluid levels of miconazole. The reason(s) for such low levels of activity was not clear, but may have been poor penetration into tissues, in vitro inactivation, and/or unusually rapid excretion. Untoward reactions from miconazole included fever, chills, nausea, vomiting, and phlebitis.

Miconazole, a membrane-active imidazole derivative, has been shown to be inhibitory in vitro against dermatophytes, a variety of yeastlike organisms including Cryptococcus neoformans and Candida species, as well as dimorphic fungi such as Blastomyces dermatitidis, Histoplasma capsulatum, and Coccidioides immitis. It is usually active in concentrations of <1 µg/ml (6).

The in vivo systemic efficacy of the drug against infections due to C. immitis has been demonstrated in experimental animals and confirmed in humans by other investigators (2, 3, 5).

A total of three patients with deep mycotic infections were treated with miconazole at the Medical College of Virginia Hospitals (MCV). Our experience with this drug is the subject of this report.

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MATERIALS AND METHODS

The diagnosis of a deep mycotic infection was made by recovery of a pathogenic fungus from tissue (patient 1, synovium and joint fluid; patient 3, subcutaneous abscess) and cerebrospinal fluid (CSF; patient 2). Susceptibility testing was performed using a previously described broth dilution technique (4). Sera and CSF samples were bioassayed for miconazole according to the agar diffusion method of Espinel-Ingroff and associates (1) which uses an isolate of Candida stella toidea with a minimum inhibitory concentration (MIC) for miconazole of 0.05 µg/ml. This system is able to detect as little as 0.5 µg of miconazole per ml.

Informal consent was obtained in every instance. Hematological, renal, hepatic, and clinical parameters were continuously monitored. The intravenous dose of miconazole used was 10 mg/kg every 8 h.

CASE REPORTS

Patient 1. A 34-year-old gardener presented to MCV with a 10-year history of intermittent pain, swelling, tenderness, and limitation of motion of the right knee joint following nonpenetrating trauma to the knee at a plant nursery. He reported no skin lesions, fever, chills, cough, sweats, or weight loss. Pertinent physical findings were confined to the right knee which revealed swelling, fixation at 30° of flexion, and a 0.5-cm draining sinus in the infrapatellar area. Microscopic examination of the serous drainage using Gram stain revealed several fusiform yeastlike organisms. Radiographs of the knee disclosed destruction of the articular cartilage and subchondral bone with loss of joint space (Fig. 1). A pure growth of Sporothrix schenckii was recovered from the drainage site. The MIC of miconazole for this organism was 0.78 µg/ml.

As a result, a trial of therapy with this agent was
begun. Five serum samples were assayed for miconazole from 1 to 9.5 h after a dose, and miconazole levels ranged from 1.35 to 4.35 µg/ml (Table 1). The drug was administered for 25 days. Despite meticulous care of the catheter and dilution of the preparation, phlebitis developed at multiple infusion sites. Thus, because of the lack of peripheral venous access, the drug was administered orally in a dosage of 20 mg/kg every 8 h for an additional 7 days without any ill effects. Miconazole serum levels of 1.7 and 1.48 µg/ml were demonstrated at 1 and 3 h, respectively, after drug ingestion and were undetectable at 6 h (Table 1). No subjective or objective improvement in the right knee occurred during treatment with miconazole. Moreover, after 32 days of therapy, S. schenckii of identical susceptibility was recovered from a diagnostic bone and synovial biopsy. Therefore, amphotericin B was employed. Sterilization of the joint space was effected with this therapy. Resolution of clinical arthritis required several weeks.

**Patient 2.** A 21-year-old white male diabetic underwent a renal transplant for diabetic nephropathy. While being treated with immunosuppressive agents, he developed severe headache and blurring of vision. *C. neoformans* was recovered from the CSF. The patient was begun on amphotericin B; less than 1 month after completing therapy, a relapse occurred. Thus he was treated with the combination of amphotericin B and flucytosine. When this treatment failed, miconazole was employed. The MIC and minimum fungicidal concentration (MFC) of miconazole were both 0.05 µg/ml against this isolate. Serum and CSF were assayed for miconazole. Two hours after a standard dose, 2.54 µg of miconazole per ml was detected in the single serum sample. Three lumbar CSF samples were obtained from 1.5 to 6 h following a similar dose. Miconazole was detected in none of these (Table 1). The patient’s disease continued to progress, and his course was complicated by obstructive hydrocephalus requiring placement of a ventriculoperitoneal shunt for decompression. The findings of repeatedly positive India ink preparations, persistent growth of *C. neoformans* from ventricular CSF, and high cryptococcal antigen titers indicated suboptimal therapy. A Rickham reservoir was thus employed in the lateral ventricle opposite the ventriculoperitoneal shunt, and miconazole was given intraventricularly in a dosage of 15 mg every 2 to 3 days while continuing the intravenous infusion. Prior to each intraventricular dose through the Rickham reservoir, the mechanical valve of the ventriculoperitoneal shunt was closed, thereby preventing immediate drainage of miconazole into the peritoneal cavity. The patient tolerated the closure for approximately 6 h. On two occasions this program produced ventricular fluid levels in excess of 120 µg/ml when samples were obtained 5 min after instillation. Ventricular fluid was also assayed for miconazole immediately prior to each intraventricular dose and from 1 to 7.5 h after an intravenous dose. Less than 0.5 µg of the drug per ml was present in each sample (Table 1). The organism was not eradicated. Significant adverse effects included phlebitis and moderately severe nausea and vomiting (especially after intraventricular treatment). Ultimately, intraventricular combined with intravenous amphotericin B was required for sterilization of the CSF. However, the patient continued to deteriorate and died in spite of this therapy. Numerous organisms compatible with *C. neoformans* were seen in postmortem sections of the brain and meninges.

**Patient 3.** A 9-year-old white male with known chronic granulomatous disease of childhood and a history of recurrent otolaryngeal and cutaneous infections was admitted to MCV because of fever, nonproductive cough, and dyspnea of 1 to 2 months’ duration. *Aspergillus fumigatus* had been isolated repeatedly from sputum as well as from two subcutaneous abscesses. Physical examination revealed a thin, tachypneic, chronically ill-appearing white male. Examination of the chest showed scattered rales and rhonchi. A fluctuant subcutaneous paravertebral mass (2 by 3 cm) was evident at the level of thoracic vertebrae eight and nine. Chest roentgenograms showed productive lesions of several ribs compatible with osteomyelitis, but no pulmonary parenchymal abnormality. The patient was treated with miconazole (Fig. 2). The MIC of miconazole against *A. fumigatus* was 0.39 µg/ml. The MFC was 0.78 µg/ml. Anticipated peak and trough serum samples were analyzed for miconazole. Less than 0.5 µg/ml was present in each (Table 1). On day 7 of miconazole, a repeat chest roentgenogram...
### Table 1. Serum and cerebrospinal fluid levels of miconazole in three patients treated for deep mycoses

<table>
<thead>
<tr>
<th>Patient</th>
<th>Organism</th>
<th>MIC/MFC (miconazole, µg/ml)</th>
<th>Dose and route (miconazole)</th>
<th>h after dose</th>
<th>Miconazole level (µg/ml)</th>
<th>Serum</th>
<th>CSF(L)b</th>
<th>CSF(V)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S. schenckii</td>
<td>0.78/100</td>
<td>10 mg/kg, i.v.</td>
<td>1.0</td>
<td>1.35</td>
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<td></td>
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<td></td>
<td>2.0</td>
<td>4.35</td>
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<td>6.5</td>
<td>1.51</td>
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<td></td>
<td>7.0</td>
<td>1.70</td>
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<td></td>
<td></td>
<td>20 mg/kg, p.o.</td>
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<td>3.0</td>
<td>1.48</td>
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<td>6.0</td>
<td>&lt;0.5</td>
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<td>&lt;0.5</td>
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<tr>
<td>2</td>
<td>C. neoformans</td>
<td>0.05/0.05</td>
<td>10 mg/kg, i.v.</td>
<td>1.5</td>
<td>&lt;0.5</td>
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<td></td>
<td></td>
<td>2.0</td>
<td>&lt;0.5</td>
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<td></td>
<td>6.0</td>
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<td></td>
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<td></td>
<td>10 mg/kg, i.v.</td>
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<td>&lt;0.5</td>
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<td></td>
<td>10 mg/kg, i.v.</td>
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<td></td>
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<td></td>
<td>15 mg intraventricularly</td>
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<td></td>
<td></td>
<td>every 2-3 days</td>
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<td></td>
<td></td>
<td>7.5</td>
<td>&lt;0.5</td>
<td></td>
<td></td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>3</td>
<td>A. fumigatus</td>
<td>0.39/0.78</td>
<td>10 mg/kg, i.v.</td>
<td>0.5</td>
<td>&lt;0.5</td>
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<td>&lt;0.5</td>
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<td></td>
<td></td>
<td></td>
<td>8.0</td>
<td>&lt;0.5</td>
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<td>&lt;0.5</td>
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</tbody>
</table>

* All serum levels were not measured after the same 10-mg/kg dose.

b CSF(L), Lumbar CSF.
cCSF(V), Ventricular CSF.
d i.V., Intravenously.
e p.o., Orally.

**Fig. 2.** Hospital course in patient with disseminated aspergillosis.

revealed new infiltrates in the right lower and left upper lung fields. Because of clinical deterioration over the next few days in the face of receiving an agent having known in vitro antifungal activity, a nosocomial bacterial pneumonia was suspected, and nafcillin and gentamicin were added to the treatment. Severe hypoxemia supervened, necessitating ventilatory support. On day 14 of miconazole therapy, a newly developed digital subcutaneous abscess was aspirated. When A. fumigatus (MIC, 1.56 µg/ml; MFC, 1.56 µg/ml) was recovered in culture from the abscess, amphotericin B was begun. Miconazole therapy was maintained because of the patient’s continued desperate condition. Definite but very slow improvement in the patient’s clinical state was noted the next week. Additionally, the patient received two isolated doses of transfer factor and daily white blood cell transfusions beginning on day 9 of amphotericin B administration and continuing for 4 days thereafter. The patient showed continued improvement and was ultimately discharged after completing 55 days of amphotericin B treatment.
DISCUSSION

Miconazole in recommended doses failed to eradicate or control infection in three patients with deep mycotic infections despite demonstrated in vitro susceptibility.

The failure of miconazole to eradicate the infection in patient 1 may have been related to subinhibitory concentrations of the drug in the synovium and/or joint space. Several attempts to document joint fluid levels of miconazole were unsuccessful. The finding of miconazole concentrations in excess of the MIC for this organism by a factor of greater than 1.5 in six of seven sera studied, irrespective of time obtained, may as inadequate serum levels a less likely explanation for the treatment failure. Alternatively, the inability to provide fungicidal serum and/or joint space levels of miconazole against S. schenckii may have prevented his cure.

The low level of miconazole produced in CSF during intravenous therapy suggested by Stevens and associates (5) is substantiated in patient 2. The persistence of low levels during concomitant intraventricular treatment was not anticipated. Poor penetration of the compound into brain and CSF may therefore only partially explain the therapeutic failure in this patient. Rapid inactivation or unusually rapid excretion may also occur. Until the pharmacokinetics of miconazole in the central nervous system are better understood, however, subinhibitory brain tissue and/or CSF levels remain the best explanation.

In patient 3, new parenchymal lung disease developed, pulmonary function deteriorated, and low serum levels of miconazole were detected despite treatment with a recommended dose of miconazole. The low peak and trough levels were not expected, although only a single specimen at each point was assayed. Nonetheless, low serum levels are the best explanation for the progression of aspergillosis. The lack of pharmacokinetic data in children makes these apparent low serum levels difficult to explain. Only after the addition of amphotericin B was significant improvement detectable. The role played by transfer factor and granulocyte transfusions in his ultimate recovery remains conjectural. Conceivably, miconazole alone could have effected a cure in the presence of normal intracellular killing mechanisms. However, if the low spumtum concentrations of miconazole reported in a patient with coccidioidomycosis (6) reflect pulmonary parenchymal levels, pulmonary aspergillosis may be refractory to treatment even in the presence of normal granulocytes. The decrease in susceptibility of the organism may have been related to suboptimal miconazole levels and may have contributed to the refractoriness of the infection.

Preliminary studies indicating the therapeutic efficacy of miconazole in coccidioidomycosis and candidiasis in laboratory animals have been done (3, 6). Using appropriate animal models, confirmatory data in other systemic fungal infections are needed. In addition, more pharmacokinetic information in human subjects is required before miconazole can be adequately evaluated in the treatment of the deep mycoses.

The therapeutic effects of miconazole were studied in three patients. The organism isolated from each individual was susceptible to miconazole in vitro. Dosages used in all three were the maximum recommended by the drug manufacturer at the time of the study.

The findings lead to these conclusions. (i) Miconazole failed to control or eradicate infection in three patients with deep mycoses despite demonstrated in vitro susceptibility of the organisms. (ii) In vitro susceptibility of S. schenckii, C. neoformans, and A. fumigatus to miconazole may not predict therapeutic efficacy. (iii) Miconazole should be used with caution in infections caused by S. schenckii, C. neoformans, and A. fumigatus. (iv) Treatment failures may have been related to inadequate tissue penetration, in vitro inactivation, and/or rapid excretion of the drug. (v) Further studies using larger doses may be indicated. (vi) Better definition of pharmacokinetics of miconazole in adults and children is needed.

ACKNOWLEDGMENTS

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LITERATURE CITED

ERRATUM

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Vol. 13, no. 6, p. 965, Abstract, line 16: “in vitro” should read “in vivo.”

Page 968, Discussion, paragraph 4, line 20: “coccidiodomycosis (6)” should read “coccidiodomycosis (5).”

Page 968, paragraph 6, line 12: “in vitro” should read “in vivo.”