Pseudallescheria boydii Infections Treated with Ketoconazole*

Clinical Evaluations of Seven Patients and In vitro Susceptibility Results

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Seven patients infected with Pseudallescheria boydii were treated with oral ketoconazole, 200 to 600 mg/day for one to 13 months. Five patients had pulmonary infections; two had skeletal infections. Improvement of pretreatment abnormalities occurred in five patients, one of whom had concurrent arthrodesis of his infected knee. The other two patients were subsequently healed by surgical resection of their pulmonary lesions. Ketoconazole appeared less active than miconazole against 22 clinical isolates of P. boydii when tested by two in vitro methods. We conclude that ketoconazole is effective treatment for some patients infected with P. boydii, although this may not be predicted by current in vitro susceptibility tests. Further experience is needed to establish the optimal use of ketoconazole with respect to its dosage, duration of administration and concurrent surgical resection.

Pseudallescheria boydii (Petriellidium boydii, Allescheria boydii, Scedosporium apiospermum) is a fungal pathogen, originally identified as an agent responsible for madura foot and more recently reported to cause diverse systemic infections, most frequently of the lungs, bones, joints, and skin, especially in immunocompromised patients. Madura foot, a chronic necrotizing infection of the distal extremities, appears most often to be the result of direct inoculation. Pneumonia is likely to be due to inhalation of the fungus and other extrapulmonary foci. P. boydii has also been reported to colonize preexisting pulmonary cavities. Except in this latter circumstance, P. boydii isolated from a site of tissue destruction is considered to represent a progressive infection and generally indicates the need for antifungal therapy.

Clinical reports suggest that amphotericin B is ineffective and P. boydii usually demonstrates marked in vitro resistance to both amphotericin B and flucytosine. Miconazole has been found to inhibit P. boydii and patients have been reported to respond to this agent. Because miconazole is administered intravenously (IV) as multiple daily infusions, it is usually not practical to continue therapy for more than several weeks, and some responding patients were found to relapse on discontinuation of their treatment.

Ketoconazole, an imidazole antifungal drug, has recently been approved for treatment of candidiasis, coccidioidomycosis, and paracoccidioidomycosis. It has the advantage of being absorbed with oral administration, thus allowing more prolonged courses of therapy. In this report, we describe treatment of seven patients with P. boydii infections. We also report susceptibility results of clinical isolates from these and other patients to both ketoconazole and miconazole.

METHODS

Since September 1978, seven patients with P. boydii infections were treated with ketoconazole at our institutions with the approval of the respective institutional review board for human subject experimentation. All patients were judged to require antifungal therapy due to the destructive nature of their clinically identified lesions. Six patients were diagnosed as having invasive infection by isolating P. boydii from a destructive lesion. The other (patient 5) had P. boydii isolated as the only pathogen on successive sputum cultures and in association with an enlarging pulmonary infiltrate. Specific abnormalities associated with the infection were identified prior to treatment. After informed consent was obtained, each patient was treated with ketoconazole (Nizoral, Janssen Pharmaceutica) at doses between 200 and 600 mg/day as a single oral morning dose. Subsequently, improvement in the pretreatment abnormalities was evaluated as evidence of drug effect. Serum concentrations of ketoconazole were determined by bioassay.

Clinical isolates of P. boydii were tested for their susceptibility to ketoconazole and miconazole by two methods as previously described. The first involved serial dilutions of drug added to a standard inoculum of P. boydii in tubes of broth. The lowest concentration of drug which prevented resultant visible growth was taken as the minimal inhibitory concentration (tub dilution MIC). The second method involved suspending the fungal inoculum in a

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Table 1—Initial and Subsequent Findings of Patients with P. boydii Infections Treated with 400 mg Ketoconazole Daily

<table>
<thead>
<tr>
<th>Age, Patient Yr/Sex</th>
<th>Underlying Disease</th>
<th>Manifestation of Infection</th>
<th>Dosage, mg</th>
<th>Duration of Treatment</th>
<th>Concurrent Resectional Surgery</th>
<th>Findings at End of Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 50/F Cardiac transplant recipient</td>
<td>Right pulmonary nodule, 3 cm diameter</td>
<td>400</td>
<td>3 mo</td>
<td>No</td>
<td>Resolution of lung infiltrate</td>
<td>36 months: no recurrence</td>
<td></td>
</tr>
<tr>
<td>2 47/M None</td>
<td>Draining ulcer at site of previous amputation, right lower leg. X-ray: osteo of distal right tibia and fibula. Bone scan: marked uptake at site of infection</td>
<td>400</td>
<td>13 mo</td>
<td>No</td>
<td>Healing of skin; resolution of edema, tenderness. X-ray: unchanged</td>
<td>No recurrence of fistulas one year after termination of treatment. Some increase of pain. Patient declined repeat biopsies.</td>
<td></td>
</tr>
<tr>
<td>3 70/F Chronic restrictive lung disease</td>
<td>Progressive diffuse peribronchial thickening</td>
<td>200</td>
<td>4 mo</td>
<td>No</td>
<td>Decrease of lung markings</td>
<td>Relapse, 4 mo after discontinuing ketoconazole. Symptoms cleared when ketoconazole was restarted</td>
<td></td>
</tr>
<tr>
<td>4 51/M Cushing’s disease</td>
<td>Left knee effusion, osteomyelitis of left medial femoral condyle</td>
<td>600</td>
<td>12 mo</td>
<td>Yes</td>
<td>Fusion of arthrodesis</td>
<td>No recurrence 14 mo after discontinuation of ketoconazole</td>
<td></td>
</tr>
<tr>
<td>5 83/M none</td>
<td>Right upper lobe infiltrate</td>
<td>400</td>
<td>6 mo</td>
<td>No</td>
<td>Resolution of lung infiltrate</td>
<td>No recurrence 5 mo after discontinuation of ketoconazole</td>
<td></td>
</tr>
<tr>
<td>6 59/F Acute myelogenous leukemia</td>
<td>Right middle lobe cavity</td>
<td>400</td>
<td>1 mo</td>
<td>Yes</td>
<td>Cavity persistent</td>
<td>No recurrence and AML in remission (remission) 38 mo after surgery</td>
<td></td>
</tr>
<tr>
<td>7 53/F None</td>
<td>Right middle lobe infiltrate</td>
<td>200</td>
<td>2 mo</td>
<td>Yes</td>
<td>No change in infiltrate</td>
<td>No recurrence 20 mo after excision</td>
<td></td>
</tr>
</tbody>
</table>

plate of agar medium in which wells were filled with serial dilutions of drug. The size of the zone of inhibition (radius of the zone minus the radius of the well)² of resultant growth surrounding each well was plotted vs drug concentration. The intercept of the vertical axis (that concentration of drug where zone size is zero) was taken as the end point.

RESULTS

Clinical Findings

Details of the results in our seven patients treated with ketoconazole are summarized in Table 1. Four improved with drug treatment alone (one of which relapsed on discontinuation of treatment), and one improved with drug therapy and concurrent surgery. Two patients failed to show evidence of response to drug therapy but are now free of disease after subsequent resection of their lesions.

Patient 1 underwent percutaneous needle aspiration of her pulmonary infiltrate (Fig 1) 11 days after its appearance. Mycelia were seen by direct examination of the aspirate, and this material grew P. boydii. After two doses of amphotericin B, the patient was treated with ketoconazole and showed complete disappearance of her infiltrate. Throughout this episode, her immunosuppressive medication—prednisone 25 mg/day, (Immuran) 15 mg/day—was continued or transiently increased.

Patient 2 had developed a chronic inflammatory process in his right foot at age 19, which had resulted in amputation above the ankle at age 32. Eight months prior to ketoconazole treatment, he developed pain, edema, discoloration, and drainage at the amputation.

![Figure 1. Chest rentgenogram of patient 1 prior to treatment with ketoconazole. Arrow indicates the infiltrate.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20381/)
decreased which complaint was positive and stump. That drainage, as well as bone biopsies before and after two months of miconazole treatment (Monostat I.V., Janssen Pharmaceutica, 30 mg/kg/day), were positive on histology and culture for \( P. \) boydii. Because miconazole had also produced no change in the appearance of the infection (Fig 2), ketoconazole treatment was begun the following month. After two months of therapy, drainage had ceased, but a bone scan was unchanged. After seven months, the lesion was painless and appeared healed (Fig 3). Many serum samples demonstrated ketoconazole peak concentrations between 2 to 4 \( \mu \)g/ml, which are in the range reported for other patients receiving this dose.7 A repeated biopsy study was declined by the patient after 13 months of therapy, and ketoconazole was discontinued because we were unable to evaluate the status of his infection. A bone scan several months before termination of therapy was unchanged, as were radiograms.

Patient 3 had been in good health except for the complaint of a persistent dry cough for many years for which she had not received specific medical therapy. One month prior to ketoconazole treatment, the patient developed dyspnea on exertion, fatigue, and decreased appetite. Also, her coughing became productive of sputum (2 tablespoons/day). A chest x-ray film showed diffuse markings which were increased as compared to an x-ray film taken the previous year. Lung washings obtained by bronchoscopy grew \( P. \) boydii as did tissue obtained by thoracotomy. Miconazole treatment was initiated but was discontinued after a few days because of phlebitis, and ketoconazole therapy was begun. She had progressive improvement in her symptoms over the ensuing four months. At that time ketoconazole was discontinued because of hepatitis (SGPT of 763 IU/L, SGOT of 751 IU/L, and alkaline phosphatase and bilirubin levels 50 percent above normal). Liver function study results worsened during the next two months and then returned to normal two months later. That this intercurrent problem was not due to ketoconazole is suggested by normal liver function study results obtained after reinstitution of ketoconazole therapy at the same
dosage. Treatment was restarted because of recurrence of her dyspnea and cough associated with a reisolation from sputa of *P. boydii*. This second course of treatment again resulted in symptomatic improvement. Eleven months later, the patient was without symptoms.

Patient 4 was found to have endogenous Cushing's disease three months prior to developing an effusion of his left knee. The previous year, the left patella had been fractured and had healed without surgery. Cultures of the initial knee aspirate grew *P. boydii* as did several cultures during and after two courses of miconazole therapy (180 g total dose), one course of amphotericin B (3.5 g total dose), and a concurrent synovectomy over the ensuing six months. An arthrodesis was performed and amphotericin B administered for two weeks. Ketoconazole was then instituted and continued for one year. There has been no recurrence.

Patient 5 was found to have a pleural-based right apical infiltrate after six weeks of anorexia, weakness, and a weight loss of 7.65 kg. Two of three sputum specimens yielded *P. boydii* in culture. After five months of therapy, appetite and activity had become normal, weight had increased 8.1 kg, and the pulmonary lesion was no longer evident. Since discontinuing therapy, there has been no evidence of relapse.

Patient 6 had developed acute myelogenous leukemia, probably as a consequence of prolonged chlorambucil therapy for ovarian carcinoma. A pulmonary infiltrate in her right middle lobe became evident while the patient was neutropenic and receiving antibacterial agents. A cavity developed, but shortly thereafter the peripheral neutrophil count returned to normal, and the patient was discharged. Two weeks later, she was readmitted to the hospital with symptoms of fatigue, night sweats, pleuritic chest pain, and a nonproductive cough. During her hospitalization, she became febrile. Bronchoscopic biopsy examination of the cavity wall demonstrated budding yeast, and cultures of material from that procedure yielded *P. boydii* and Candida (not *C. albicans*). Ketoconazole therapy was instituted but resulted in no symptomatic improvement or change in appearance of her cavity, despite a serum concentration three hours after ketoconazole administration of 3.6 µg/ml. After one month of therapy, a right middle lobectomy was performed. Cultures obtained from the surgical specimen grew Candida and *P. boydii*. No further antifungal therapy was administered. Her leukemia has remained in remission for over three years, and there has been no recurrence of the *P. boydii* infection.

Patient 7 was otherwise in good health when a mild cough led to a chest x-ray examination that demonstrated a right middle lobe infiltrate. Thoracotomy was performed, tissue from which yielded *P. boydii*. Because the lesion had not been excised completely during this procedure, ketoconazole was administered without demonstrable change in the radiologic appearance of the lesion. Subsequently, a complete lobectomy was performed, and cultures of tissue from that procedure again grew *P. boydii*. After 20 months, there has been no evidence of recurrence.

In vitro Fungal Susceptibility Testing

Twenty-two isolates were tested by the tube dilution method against miconazole and 14 against ketoconazole; by the agar well method, 11 and ten strains were tested with the respective drugs. The cumulative susceptibility results are shown in Figure 4. The MIC₉₀ (that drug concentration inhibiting 90 percent of the isolates) was 0.195 and 1.56 µg/ml for miconazole by the tube dilution and agar well methods and for ketoconazole 6.25 and 12.5 µg/ml. If MIC results are used in selecting antimicrobial agents, the MIC₉₀ is often considered. These values are 0.78 and greater than 50 µg/ml for miconazole, respectively, but for ketoconazole were greater than 50 and 25 µg/ml, respectively. Isolates from patients 1 and 2, tested by the agar

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20381/)
well method, showed inhibition by ketoconazole at 8.0 and 2.7 μg/ml, respectively. The isolate from patient 3, tested by the tube dilution method, was sensitive to 3.13 μg/ml. Two isolates of Scedosporium apiospermum (the asexual stage) have also been tested, with results in keeping with those given for P. boydii.

Although there was divergence in results between the two methods, with both methods, the miconazole appeared more active than ketoconazole against this pathogen. This was uniformly true when the activity of the two antifungal agents was compared for 15 isolates by one or the other method (Fig 5). By either method and in all cases, miconazole appeared more active than ketoconazole in vitro.

**DISCUSSION**

The patients who had improvement during ketoconazole therapy each represent differing settings in which *P. boydii* is found as a pathogen. The first was immunosuppressed and acutely developed a pulmonary infiltrate which led to specific therapy within days after onset of its appearance. Her infection has not recurred after only three months of treatment with over three years of posttherapy surveillance. In general, however, it may be prudent to treat patients with ketoconazole for more prolonged periods than this patient appeared to require. Ketoconazole has frequently not been curative for patients with other mycoses who appeared to be cured by several objective measures, only to relapse later.  

In addition, relapses of *P. boydii* infections have been noted after miconazole treatment. This appeared to occur with our patient 3 as well. In contrast to the acute infection of patient 1, the second patient displayed a chronic, focal infection of a distal extremity which had been present for at least eight months and probably for many years. Drainage from this lesion ceased after two months of ketoconazole therapy, where no apparent response had been evident after a prior course of miconazole of the same duration. The third patient had increased respiratory tract symptoms superimposed on a chronic fibrotic pulmonary process. Histologic examination of an open lung biopsy specimen demonstrated bronchial inflammation, suggesting that her infection did not involve the alveolar parenchyma. Her symptoms and chest x-ray film cleared with treatment, worsened after therapy had been discontinued, and improved again when ketoconazole therapy was resumed. The fourth patient with Cushing’s disease developed his knee infection, probably by hematogenous seeding, relatively soon after trauma to that joint. Although he has had no recurrence of his infection 12 months after discontinuing ketoconazole therapy, the specific contribution of drug therapy is difficult to assess, because of his subsequent bilateral adrenalectomy and the arthrodesis performed concurrently. Clearly, surgical resection is not always effective, as judged by the relapse of patient 2 after his amputation.

The value of resection of pulmonary infections for some patients is underscored by the course of our two patients who failed ketoconazole therapy. Our sixth patient was receiving immunosuppressive therapy for her acute myelogenous leukemia when she developed her infection. However, her leukemia was in remission and her peripheral blood neutrophil count was normal throughout her relatively short treatment course of one month. Her infection had already created a pulmonary cavity prior to beginning ketoconazole treatment, and surgical cultures after treatment yielded other organisms as well as *P. boydii*. Our seventh patient had no factors which complicated her treatment failure. Both patients have had no evidence of *P. boydii* infection following surgical resection.

The role of the laboratory in aiding in management decisions for patients with *P. boydii* infections requires critical evaluation. That the clinical laboratory be able to distinguish *P. boydii* from Aspergillus species and other more common molds is important, since *P. boydii* infections would not be expected to respond to amphotericin B, the agent that otherwise might be used. However, results from antifungal in vitro susceptibility tests should be used with caution in selecting therapeutic agents. The improvement demonstrated by some of our patients contrasts with the marginal in vitro sensitivity to ketoconazole. Although *P. boydii* appears less sensitive to ketoconazole than do several other fungi as reported elsewhere, there are few data available to assess the correlation between in vitro results and treatment outcome. This lack of correlation is compounded by the lack of standardized testing methods.
Our experience indicates that ketoconazole may have a role in the treatment of P. boydii infections. Whether higher doses may improve treatment results with this agent will require further studies. Pursuit of this question seems warranted due to the destructive nature of such infections, even in light of the hormonal perturbations noted with higher ketoconazole doses. The value of ketoconazole, relative to miconazole or to surgical resection, also remains to be determined.

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