Fluconazole in the Treatment of Persistent Coccidioidomycosis*

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Fluconazole is one of the new antifungal triazoles undergoing clinical trials. We used fluconazole at a dose of 50 or 100 mg/day in an open trial for the treatment of patients with persistent coccidioidomycosis. Fourteen patients were enrolled and treated for a mean of 13±7 months. Two failed to respond. Of the 12 who responded, one reactivated while being treated, and one died of myocardial infarction after successful treatment of his fungal infection; six had relapses from nine days to 15 months after treatment was stopped. Only four patients are asymptomatic at a mean of 14±3 months after cessation of treatment. Fluconazole is well tolerated at this dose. In view of its low toxicity, the partial clinical efficacy observed, and the high recurrence rate of chronic coccidioidal infection, it would be justified to try higher doses. (Chest 1990; 97:666-69)

Treatment of chronic coccidioidomycosis can be difficult. There are only a few effective drugs. The best established drug, amphotericin B, must be administered parenterally and is highly toxic. Miconazole was the first imidazole to be tested against Coccidioides immitis. The use of miconazole is limited by the fact that it must be administered parenterally, the carrier solvent is toxic, and since the drug is cleared rapidly, it must be administered several times each day. Ketoconazole was the first orally absorbed azole shown to have activity against C immitis. Ketoconazole is often effective in extrameningeal infection; however, its usefulness is limited by a high rate of recurrence after treatment is discontinued. Attempts to reduce rates of relapse by using higher doses have been frustrated by the occurrence of toxic effects.

Chemical manipulation of the azole structure has provided several new antifungal agents. Itraconazole is currently undergoing evaluation and appears to have promise. Fluconazole is a triazole that is the first of these agents not highly bound to protein. This probably accounts for its large volume of distribution and its excellent penetration into the cerebrospinal fluid. Fluconazole has good activity in murine coccidioidomycosis but has not been previously tested in humans. For these reasons, we undertook a clinical evaluation of the toxicity and efficacy of fluconazole in patients with persistent coccidioidomycosis.

Materials and Methods

Patients were enrolled in this study at the University of California San Diego Medical Center and the VA Medical Center from July 1986 to March 1987. Participation in the study was offered to all known patients who had a diagnosis of coccidioidomycosis proven by culture or histology, and who had persistent pulmonary or disseminated infection. Patients with primary pulmonary coccidioidomycosis were excluded. Some patients had previously failed to respond to or reactivated following treatment with amphotericin B or ketoconazole. All patients had either pulmonary infection for more than a year or disseminated disease with cultures positive for C immitis or spherules seen on biopsy in conjunction with serum complement-fixation antibodies against C immitis antigens. Patients with immunosuppressive disease, hepatitis, or pregnancy were excluded.

Patients

Fourteen patients met the criteria to be enrolled in this series. The age range was 25 to 83 years; all patients but one were older than 30 years, and four were over 60 years old. There were ten men and four women. Nine patients were white, three were Hispanic, and one each was black and American Indian. Coccidioidal infection was confined to the lungs in four patients, was extrapulmonary in seven patients, and involved both in three patients. The pulmonary involvement consisted of a single chronic cavity in two patients, chronic fibrocavitary disease in two patients, or hilar and mediastinal adenopathy (one patient also had an infiltrate) with dissemination to soft tissue in three patients. No patient had primary pneumonia, which is often self-limited. The sites of extrapulmonary dissemination were multiple in most cases and were as follows: skin or soft tissue, five patients; visceral organs, five patients; lymph nodes, four patients; and bone or synovium, two patients. Soft tissue involvement was adjacent to cutaneous lesions in five patients and to surgical wounds in two patients. In one case, there was infection of a deep wound following nephrectomy for renal cell carcinoma. The involved visceral organ was the liver in one, the peritoneum in two, and the epididymis in two patients. Of the two patients with skeletal involvement, one had several bony lesions, and one had synovitis of the knee.

Treatment

Patients were started on 50 mg of fluconazole per day. If there was not a satisfactory clinical response in two weeks to ten months, the dosage was increased to 100 mg/day. In each case the medication was administered once per day in the morning. Patients were

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Fluconazole in Persistent Coccidioidomycoysis (Catanzaro, Fierer, Friedman)
Coccidioides Serologic indicated, was Cr radiographic and serum counts; complete counted. Examined enlarge, soft to more. Large Size Media Stinal Distribution Fever as the mean 2.8 dosage, 0.3. The culture. had fluconazole therapy. In no case did the level rise above twice normal, and it usually declined to baseline after a few months of therapy. One patient had persistently elevated SGOT and SGPT concentrations.

Coccidioides immitis was identified histologically or by culture in all patients at the start of treatment. Follow-up cultures were positive in the two patients with failure of treatment and were negative in five of the 12 responders. In seven patients, follow-up cultures were not done because rebiopsy was not clinically indicated, and there was no noninvasive way to obtain material for culture.

Serologic response to coccidiodin was monitored monthly using the complement fixation assay. Titers before treatment were high; after treatment, titers were significantly lower. In two of the ten responders who had elevated titers initially, there was a sevenfold drop in titer; in four, there was a twofold drop during treatment (Table 1).

Roentgenograms were made as clinically indicated to assess the response to treatment. Serial roentgenograms were read systematically by a chest radiologist (P.F.) and were scored using our radiographic criteria. The patient with infiltrative disease had clearing of most of his infiltrates. The radiographic score at the start of treatment was 5; at the end of treatment, it was 2. The radiographic score on the four patients with cavitary or fibrocavitary disease did not change; however, we did observe minimal improvement, including clearing of intracavitary fluid, clearing of pericavitary infiltrates, and reduction in the thickness of cavity walls. The improvements noted in cavitary lesions were always minimal and incomplete and of uncertain significance, since these changes can occur spontaneously.

Subsequent Course

Of the 12 who initially responded, only four remained free of coccidiodial disease. These patients have been followed for 10, 13, 15, and 18 months. One patient died of a myocardial infarction at the end of successful treatment of his fungal infection. Six of the 11 surviving responders had a relapse nine days to 15 months after treatment was stopped. Only one

RESULTS

Clinical response was favorable initially in 12 of 14 patients. The clinical scores of each patient at the beginning and end of treatment are listed in Table 1. The mean score before treatment for the 12 responders was 2.8 ± 7; their mean score after treatment was 0.08 ± 0.3. Resolution of visible lesions was relatively prompt. These 12 patients took fluconazole for from 5 to 23 months (mean, 13 ± 7).

Two patients had failure of treatment. Patient 6 presented with a four-month course of pneumonia followed by multiple disseminated lesions of the skin, soft tissue, and bones. She was given 50 mg/day for two weeks and then advanced to 100 mg/day. Despite treatment for ten weeks, old lesions continued to enlarge, and she developed new cutaneous lesions.

Patient 14 had chronic synovitis of the knee. He received 50 mg/day for four weeks and was then advanced to 100 mg/day. Despite treatment for three months, he remained symptomatic. Analysis of the synovial fluid showed persistent inflammatory changes, and C immitis continued to be found in the aspirated fluid.

In general, the drug was well tolerated. Compliance was excellent. Two patients complained of possible drug-related side effects, headaches in one and memory loss in another. In no case was the drug stopped because of intolerance. The only abnormality encountered in the monthly laboratory tests was minimal elevation of the gamma-glutamyl transference level in seven patients before treatment, which became more abnormal with fluconazole therapy. In no case did the level rise above twice normal, and it usually declined to baseline after a few months of therapy. One patient had persistently elevated SGOT and SGPT concentrations.

Coccidioides immitis was identified histologically or by culture in all patients at the start of treatment. Follow-up cultures were positive in the two patients with failure of treatment and were negative in five of the 12 responders. In seven patients, follow-up cultures were not done because rebiopsy was not clinically indicated, and there was no noninvasive way to obtain material for culture.
responder suffered a relapse while still receiving fluconazole. The clinical courses of the patients who had a relapse are summarized briefly.

Patient 3 had longstanding fibrocavitary disease. He previously had responded to amphotericin B, but suffered a relapse. A similar scenario followed treatment with ketoconazole. He then responded well to treatment with fluconazole (50 mg/day), with resolution of all pulmonary symptoms but minimal improvement in his roentgenogram. Eight months after fluconazole had been discontinued, the patient developed fever, weight loss, and a productive cough, and C. immitis was again recovered from his sputum.

Patient 4 had longstanding fibrocavitary pulmonary disease and was treated for 12 months at a dose of 50 mg/day. She became free of symptoms, and cultures of sputum were repeatedly negative. Nine days after treatment was stopped, she suffered recurrence of cough, sputum, and hemoptysis. A sputum culture was positive for C. immitis.

Patient 5 presented with fever, weight loss, a cutaneous lesion, cervical adenopathy, pulmonary symptoms, and an infiltrate with hilar adenopathy on chest roentgenograms. He responded well to a course of treatment of 50 mg/day for 4.5 months. Two months after fluconazole was discontinued, he developed coccidioidal meningitis.

Patient 7 had cervical and azygous adenopathy, as well as epididymitis. He responded to treatment with resolution of his lesions. Four months after discontin-

Table 1—Data on Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Site of Infection</th>
<th>Months of Treatment</th>
<th>Clinical Score</th>
<th>C. immitis*</th>
<th>Complement Fixation Titer†</th>
<th>Follow-Up, mo‡</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>50 mg</td>
<td>100 mg</td>
<td>Total</td>
<td>Start</td>
<td>End</td>
</tr>
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<td>10</td>
<td>19</td>
<td>3</td>
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<td>17</td>
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</tr>
<tr>
<td>3</td>
<td>Fibrocavitary</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Fibrocavitary</td>
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<td>12</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Pulmonary infiltrate; hilar adenopathy; disseminated disease</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>0</td>
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<tr>
<td>6</td>
<td>Skin; soft tissue; mediastinal adenopathy</td>
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<td>1.5</td>
<td>2</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>Epididymis; cervical lymph node; azygous lymph nodes</td>
<td>10</td>
<td>11</td>
<td>21</td>
<td>3</td>
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<tr>
<td>8</td>
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<td>23</td>
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<tr>
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<td>Abscess after nephrectomy</td>
<td>6</td>
<td>16</td>
<td>22</td>
<td>3</td>
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</tr>
<tr>
<td>12</td>
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<td>6</td>
<td>3</td>
<td>9</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
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<td>5</td>
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</tr>
<tr>
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<td>Synovitis of knee</td>
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<td>3</td>
<td>4</td>
<td>2</td>
<td>2</td>
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</tbody>
</table>

*POS, C. immitis grown on culture; H-POS, spherules identified on histologic examination but no cultures performed; and NEG, fungal cultures performed but C. immitis not grown.
†Expressed as highest dilution of serum that completely binds complement in presence of coccidioidin.
‡NA, Not available; and M1, myocardial infarction.
uation of fluconazole, a new cervical lymph node enlarged. It was biopsied, and the culture grew \textit{C immitis}.

Patient 10 had a longstanding soft tissue infection adjacent to the greater trochanter. The lesions were drained surgically, and the patient was treated with fluconazole at 50 mg/day for 12 months. All symptoms cleared, and radiographic abnormalities improved. Six weeks after discontinuation of fluconazole, local pain recurred. Needle aspiration yielded \textit{C immitis}.

Patient 11 initially responded, but after 22 months of treatment, a deep abscess wound reopened. \textit{Staphylococcus aureus} and \textit{C immitis} were recovered from the wound.

Patient 12 had peritonitis and several cutaneous lesions. Treatment resulted in resolution of the cutaneous lesions. Eight months after the drug was stopped, one cutaneous lesion recurred, and \textit{C immitis} was found on biopsy. Peritonitis did not recur.

\textbf{DISCUSSION}

Fluconazole is one of the new imidazoles undergoing clinical trials for the treatment of fungal infections. We used fluconazole at a dose of 50 or 100 mg/day for the treatment of patients with persistent or disseminated coccidioidomycosis. Twelve of 14 patients had an initial favorable response, with definite improvement of clinical signs and symptoms of coccidioidal infection; however, five of 11 surviving patients suffered reactivation of their infections 9 days to 15 months after fluconazole was stopped.

Comparison of treatments for coccidioidomycosis is difficult. The disease has many manifestations, and the course is highly variable. Controlled comparisons therefore require large numbers of patients. While this study was not a controlled trial, the criteria used for entry of patients and the results allow us to conclude that fluconazole is active against \textit{C immitis}. Most patients had a good subjective clinical response. There was also objective evidence of antifungal activity. In five of seven who had follow-up cultures, the cultures became negative. Eight of ten patients who responded clinically and had elevated serologic values prior to treatment had reductions in coccidioidal complement fixation titers. Seven patients’ lesions completely resolved and could not be biopsied; however, the changes in chest roentgenograms in five patients with pulmonary involvement were minimal, and the drug’s effect was difficult to detect because all but one of these had chronic pulmonary infection in which many of the changes visualized were structural and unlikely to be restored to normal (eg, fibrocavitary lesions).

Long-term cure of chronic or disseminated infection is a difficult goal to achieve in coccidioidomycosis. It was clearly not achieved in this series, despite largely favorable initial results. There was an unacceptably high rate of relapse, even after one to two years of treatment. It is particularly troublesome that a fall in complement fixation titer or a negative fungal culture was noted both in patients who later had a recurrence and in those who did not. Two of the patients who later suffered a relapse had no detectable complement fixation antibody when treatment was stopped. These tests are useful for assessing response to therapy, but neither laboratory “improvement” nor suppression of clinical manifestations necessarily means that the infection is eradicated.

In this series of patients, at doses of 50 or 100 mg/day, fluconazole was well tolerated for extended periods, causing little or no adverse effects reported by the patients. Laboratory evidence of adverse effects was confined to minimal changes in hepatic function in patients who already had some abnormality at the time fluconazole was started. In view of this minimal toxicity and the evidence that fluconazole has substantial antifungal activity, it is recommended that a higher dosage be evaluated.

\textbf{REFERENCES}