High-Dose Itraconazole in the Treatment of Severe Mycoses

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Received 20 June 1990/Accepted 26 January 1991

Eight patients with systemic mycoses and with prior treatment failures were treated with itraconazole (600 mg/day) for a mean duration of 5.5 months. All six patients without AIDS experienced improvement or stabilization of their fungal infections while receiving high-dose itraconazole, although two patients later experienced treatment failures, one by relapse and one by progression, on lower doses. Treatment failures also occurred in the two patients with AIDS and cryptococcal meningitis. The failures were associated with low serum itraconazole concentrations (<2.5 μg/ml) in both patients. All other patients had mean trough levels in serum above 5 μg/ml. One patient who was improving on 600 mg/day developed a progressive infection after reduction of the dose to 400 mg/day. Side effects included reversible adrenal insufficiency in one patient; severe hypokalemia, mild diastolic hypertension, and rhabdomyolysis in one patient; mild hypokalemia and hypertension in four other patients; and breast tenderness in one patient. The mean decrease in serum potassium during treatment was statistically significant (P = 0.05). Selected patients with severe systemic mycoses may benefit from prolonged high-dose itraconazole treatment. However, 600 mg/day may be approaching the upper limits of acceptable dosing for long-term treatment.

Itraconazole, a new oral triazole antifungal agent, has been used investigationally for several years. It is more potent and has a wider spectrum of activity than ketoconazole in vitro and in vivo (3, 7, 32, 36, 37). Clinical responses have been reported in patients with systemic mycoses, including coccidioidomycosis, sporotrichosis, chromoblastomycosis, and aspergillosis. Usual treatment regimens have included daily dosing at 400 mg or less (2, 4, 8, 21, 23, 28, 29, 34). Few adverse effects have been noted in the treatment of human mycoses with doses of up to 400 mg/day (2, 4, 8, 21, 23, 28, 29, 34, 36).

The activity of antifungal azoles is based on their interference with certain fungal cytochrome P-450 enzymes. This activity impairs the synthesis of ergosterol and secondarily disrupts a variety of metabolic processes (3, 9, 38). Fungal cytochrome P-450 enzymes are more susceptible than are those of mammalian cells; however, ketoconazole and other imidazoles inhibit mammalian cytochrome P-450 enzymes in multiple organs, including the liver, testes, and adrenal glands (9, 15, 19, 25–27, 30, 35, 38). In contrast to ketoconazole, itraconazole has no significant effects on testicular and adrenal hormones during treatment with doses of up to 400 mg/day (9, 19, 25–27, 30, 33, 35). The lack of these effects may be due to a more selective inhibition of P-450 enzymes in fungal cells than in mammalian cells by itraconazole (19, 36).

Over the past 2 years, we have treated eight patients with itraconazole at 600 mg/day for serious or life-threatening fungal infections. All eight had experienced treatment failures on lower doses of itraconazole or other antifungal agents, and we hoped that the higher dose would be successful. This experience forms the basis of this report.

MATERIALS AND METHODS

All patients had systemic fungal infections judged to be severe or life-threatening by the investigators. All gave informed consent for investigational treatment with 600 mg of itraconazole per day. Diagnosis of the fungal infections required confirmation by histopathology (characteristic organisms seen in the appropriate clinical specimens) and/or positive fungal cultures. All patients had received prior systemic antifungal therapy and were considered to have experienced treatment failures, as defined below, with one exception. Although this patient had experienced disease progression on amphotericin B (AMB) therapy, in retrospect his response to 400 mg of itraconazole per day could be classified as stabilization. Dose escalation to 600 mg/day was based on radiographic abnormalities of nonfungal origin. Prior systemic antifungal therapy was not standardized. In different patients, this therapy included one or more courses of treatment with AMB, ketoconazole, miconazole, fluconazole in combination with AMB, or lower doses of itraconazole. All other systemic antifungal therapy was discontinued before therapy with 600 mg of itraconazole per day was started (300 mg with breakfast and 300 mg with an evening meal or snack).

The clinical course was monitored biweekly for the first month and then monthly in all but one patient. This patient, who had received lower doses of itraconazole for several years, was monitored every 3 months. At each visit, symptoms were assessed and toxicity was monitored by determining complete blood counts, serum electrolytes, urea nitrogen, creatinine, bilirubin, alkaline phosphatase, and amino transferases (serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and ɣ-glutamyltransferase) and by performing a urinalysis. Culturing was also done when procedures for obtaining specimens were not dangerously invasive.

An 8-h corticotropin stimulation test was performed on each patient after at least 1 month of treatment with 600 mg of itraconazole per day (24). The adrenal cortisol response to an 8-h infusion of 40 U (400 μg/500 ml) of synthetic corticotropin (Cortrosyn) was measured at the baseline and 0.5, 1, 2, 4, and 8 h into the infusion. A concurrent 24-h urine specimen for the measurement of free cortisol, 17-hydroxycorticoids, and 17-ketosteroids was also collected.

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After at least 1 month of treatment with 600 mg of itraconazole per day was completed, concentrations of itraconazole in serum were measured over a 24-h period. Patients were usually hospitalized the evening prior to this evaluation. Following the morning dose of 300 mg, serum specimens were taken at 0, 0.5, 1, 2, 4, 8, 12, and 24 h. To permit this, we did not administer the evening dose on the day of evaluation. Serum aliquots were frozen until analyzed. Bioassay methods were used to measure itraconazole concentrations, reported as micrograms per milliliter (1).

Treatment responses were classified as improvement, stabilization, or failure. Improvement was defined as the resolution of one-half or more of the symptoms and signs of infection and negative follow-up cultures (when culturing was done). Stabilization was defined as the improvement in the symptoms and signs of infection but the resolution of less than one-half of these and no mycological, histopathological, or clinical evidence of a progressive infection. Failure was defined as progression in the symptoms or signs of infection, clinical relapse following an initial response to therapy, or persistent clinical symptoms or positive fungal cultures after several months of antifungal therapy. Because of the number of different mycoses included in this study, it was difficult to define treatment responses by more specific criteria. However, additional response parameters are included in the text and Table 1 for individual patients.

Blood pressure and the potassium concentration in serum were evaluated in patients before and during treatment with high-dose itraconazole. Statistical analysis was performed with a two-factor analysis of variance. A comparison was made between pretreatment blood pressures and all those obtained during treatment by medical personnel prior to the institution of antihypertensive therapy. Pretreatment blood pressures included consecutive values (up to six) recorded in the case record before therapy with 600 mg of itraconazole per day was started (mean number of pretreatment values per patient, 3.0). Hypertension was defined as a pressure greater than or equal to 160/90 mm Hg for those under 45 years of age and 160/95 mm Hg for those over 45 years of age. An additional comparison was made between pretreatment serum potassium concentrations and those obtained during treatment with 600 mg of itraconazole per day prior to the institution of potassium replacement therapy. Pretreatment serum potassium concentrations were the values obtained immediately before therapy with 600 mg of itraconazole per day, except in one patient (no. 7). The pretreatment serum potassium concentration in this patient was the mean of the concentration obtained immediately prior to the initiation of 600 mg of itraconazole per day and the concentration obtained 1 month earlier (considered more representative of this patient’s usual state of potassium balance).

**RESULTS**

**Clinical presentation.** The mean age of the eight patients was 31 years (range, 18 to 72 years). Seven were male. Two patients had AIDS. All patients were considered to have experienced prior treatment failures, two by a relapse, four by disease progression during treatment, and two by a lack of an adequate response. Of the last two patients, one (no. 8) had improved while on itraconazole at 400 mg/day but had had persistent positive cultures after 6 months and then had experienced disease progression while on fluconazole. The other (no. 3) had experienced disease progression during extensive debridement and treatment with high doses of AMB but appeared to have stabilized on 400 mg of itraconazole per day with persistent signs but negative cultures. The dose was escalated to 600 mg/day in response to pulmonary abnormalities later documented as nonfungal in origin. Table 1 contains additional data regarding individual clinical presentations and treatment responses.

Two patients (1 and 2) had phaeohyphomycosis caused by Bipolaris hawaiiensis and were included in prior reports (20, 31). In both, disease involved paranasal sinuses, with direct invasion of surrounding structures. One patient developed blindness because of optic nerve invasion which occurred during AMB treatment (total dose, 3.9 g). The infection also extended into the frontal lobe. A detailed description of the clinical presentations is reported elsewhere (20). The other patient relapsed following courses of AMB and miconazole. He had involvement of soft tissues and bones near the orbit.

Four patients had coccidioidomycosis. Two patients (5 and 8) had infections confined to the lungs and pleura. In another patient (no. 4), disease was found in the lungs and lymph nodes, and a lymphocutaneous fistula from a rib was suspected because of focal increased gallium uptake. The other patient (no. 3) had a very chronic (>8 years) infection of laryngeal structures and cervical lymph nodes. Prior therapy in these four patients included courses of AMB (three patients), ketoconazole (three patients), or lower doses of itraconazole (two patients).

Both patients with AIDS had cryptococcal meningoitis. In one patient (no. 6), a disseminated infection progressed with persistent positive cultures during prior courses of fluconazole (100 mg daily for 2 months) and AMB (total dose exceeding 2 g) treatment. In the other patient (no. 7), symptoms progressed and cryptococcal antigen levels in cerebrospinal fluid continued to increase despite courses of combined AMB and flucytosine (3 weeks) and fluconazole (100 mg daily for 2 months) treatment.

**Treatment responses.** In the eight patients, the mean duration of treatment with high-dose itraconazole was 5.5 months (range, 3 to 16 months). Both patients (1 and 2) with phaeohyphomycosis experienced stabilization of their infection on high-dose itraconazole. Treatment at this dose was continued for 8 and 4 months, respectively, and then reduced to 400 mg/day. After 3 years of itraconazole, one patient (no. 1) remained stable on 400 mg/day as chronic maintenance therapy. The other patient (no. 2) completed a total of 3 years of itraconazole with no evidence of relapse at a 3-month follow-up.

Three of the patients with coccidioidomycosis clinically improved during high-dose itraconazole treatment, but two experienced subsequent treatment failures. In two patients (4 and 5), symptoms resolved during high-dose therapy. Treatment at this dose was continued for 4 and 3 months, respectively, and then reduced to 400 mg/day. Treatment was discontinued after 8 months at the reduced dose (or a total of 1 year of itraconazole) in patient 4. He subsequently relapsed 1.5 years after discontinuation. Patient 5 received an additional 3 months of treatment at the reduced dose. He had no evidence of an active infection 10 months after discontinuation of treatment. Another patient (no. 3) showed improvement in symptoms and signs during prior treatment with itraconazole at 400 mg/day. Cultures reverted to negative. In retrospect, dose escalation to 600 mg/day was not based on failure of prior treatment. The patient continued on itraconazole at 600 mg/day for 16 months. The last patient with coccidioidomycosis (no. 8) responded to high-dose itraconazole with the resolution of symptoms, the conversion of sputum cultures to negative, and a reduction in the size of cavities (as determined by chest radiographs). High-
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**TABLE 1**: Clinical presentations and treatment response of patients.
dose treatment was continued for a total of 5 months. The dose was then reduced to 400 mg/day because of symptomatic hypoadrenalism. On the reduced dose of 400 mg/day, symptoms again progressed and sputum cultures reverted to positive.

Both patients with AIDS and cryptococcal meningitis experienced progression of their fungal infections during treatment with high-dose itraconazole. In one, the progression of the infection continued despite other therapeutic attempts and ended with death. The other stabilized with protracted AMB treatment.

**Toxicity.** None of the eight patients experienced gastrointestinal symptoms attributable to itraconazole. No elevations in hepatic function values over baseline values were noted.

All patients underwent 8-h ACTH stimulation (Fig. 1). Seven patients (1 through 7) had normal responses in comparison with previously published data on responses before and during treatment with lower doses of itraconazole (24). Patient 8 had a slightly reduced cortisol response 2 weeks after beginning high-dose itraconazole (Fig. 1, curve a). Routine evaluation after 1 month of 600 mg of itraconazole per day revealed a more blunted response (Fig. 1, curve c). At 6 weeks, the patient experienced weakness, fatigue, orthostatic dizziness, intolerance of sun and heat, and edema prominent in the face and lower extremities. The cortisol response at that time (Fig. 1, curve d) was markedly blunted (below 2 μg/dl). Urine-free cortisol was present at <5 μg/24 h (normal, unstimulated control level, >5 μg/24 h), and 17-hydroxycorticosteroids were present at 0.3 mg/24 h (normal level, 3 to 10 mg/24 h). Dose reduction to 400 mg/day was associated with a resolution of the symptoms associated with adrenal insufficiency and an improved cortisol response (Fig. 1, curve b).

After 8 months of treatment with itraconazole at 600 mg/day, patient 1 was noted to have hypokalemia (potassium level, 2.5 meq/liter), hypertension, and mild edema. Supine and standing aldosterone concentrations in serum were mildly depressed (supine, <2.5 ng/dl [normal, 1 to 16 ng/dl]; standing, 3.2 ng/dl [normal, 4 to 31 ng/dl]) in this patient. Edema was also noted in four other patients. For the entire group, there was a significant association of itraconazole treatment with reduced serum potassium levels \((P = 0.05)\). Hypokalemia could not be attributed to other concurrent medications. Although there was no significant difference between blood pressure values before and during treatment for the group, two patients (4 and 5) had significant elevations in blood pressure during treatment as compared with pretreatment. This effect could not be attributed to other concurrent medications.

One patient developed mild breast tenderness during treatment with 600 mg of itraconazole per day. The testosterone concentration in serum was 306 ng/dl (normal concentration, >280 ng/dl).

**Itraconazole concentrations in serum.** The itraconazole concentrations observed in serum are indicated in Fig. 2. Patient 7 had itraconazole levels consistently below 2 μg/ml. Patient 6 had an isolated value of 2.23 μg/ml. All other patients had 12-h postdose concentrations in serum above 5 μg/ml. Because of slow clearance, the 24-h period of observation did not allow the calculation of individual pharmacokinetic parameters. In four patients, there was a delayed increase in the concentrations (occurring more than 4 h postdose).

**DISCUSSION**

Itraconazole is an important addition to the rather limited selection of systemic antifungal agents available today. The wider spectrum of activity and greater potency are advantages over ketoconazole (3, 7, 32, 36, 37). Itraconazole therapy has been effective in some patients who have experienced failures of prior therapy with either ketoconazole or AMB (8). Prior experience with ketoconazole dem-

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**FIG. 1.** Serum cortisol responses to 8-h infusions of synthetic corticotropin during treatment with itraconazole (600 mg/day). The responses of patients 1 through 7 are indicated by the shaded area between the highest (High) and lowest (Low) cortisol responses, with the mean response being represented by the curve labeled Mean. The responses of patient 8 are indicated by the curves labeled a through d. a, Response prior to the dose increase to 600 mg/day; c, response after 4 weeks of itraconazole at 600 mg/day; d, response after 6 weeks of itraconazole, with symptomatic hypoadrenalism; b, response only 3 days after the dose reduction to 400 mg/day.
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FIG. 2. Serum itraconazole concentrations as measured by a bioassay after 1 month of treatment with 600 mg/day. The serum itraconazole concentrations as measured at intervals over a 24-h period following the morning dose (the evening dose was withheld) are indicated, with lines connecting the values of individual patients. Only an isolated concentration was available for patient 6, who ultimately did not respond to treatment with itraconazole at 600 mg/day. Patient 7 had concentrations consistently below 2 μg/ml and also did not respond to treatment.

Demonstrated that some infections, especially those involving the central nervous system, required doses of up to 1,200 mg/day or more (5, 10). These high doses were associated with significant gastrointestinal and endocrine system side effects.

Despite the potency of itraconazole, we were concerned that unusually high doses might be required to arrest serious fungal infections in certain patients. We report here encouraging results with 600 mg of itraconazole per day as a salvage-type regimen in a small number of patients with serious or refractory fungal infections that did not respond to various prior treatment regimens.

All six patients without AIDS experienced improvement or stabilization of their fungal infections while receiving high-dose itraconazole. This result was particularly impressive in the two patients with life-threatening phaeohyphomycosis. One of these patients had suffered invasion of the frontal lobe, and the other had suffered disease progression in a site adjacent to the cerebral cortex. All six patients had mean trough levels in serum above 5 μg/ml. One patient improving on 600 mg/day relapsed with a progressive infection after dose reduction to 400 mg/day.

Two patients with treatment failures in this study had AIDS and cryptococcal meningitis. One factor in the poor outcome of the two cryptococcal meningitis patients may have been poor itraconazole penetration into the cerebrospinal fluid (22). However, the arrest of progressive disease in patient 1 (phaeohyphomycosis) suggested that itraconazole is efficacious in some central nervous system infections. Additionally, favorable results in the treatment of cryptococcal meningitis in AIDS patients have been noted in other studies (6, 39).

Poor drug absorption may be a more likely reason for the failures in the cryptococcosis patients. One of these patients had serum itraconazole concentrations consistently below 2 μg/ml. Only a single (also low) itraconazole concentration in serum was available in the other patient. Impaired gastric acid secretion is a common finding in patients with AIDS (16). Like ketoconazole absorption, itraconazole absorption may be influenced by gastric acidity, and absorption may have been impaired by reduced gastric acidity. This effect has been documented for ketoconazole (17). A similar correlation between low levels in serum and unfavorable outcomes with itraconazole therapy was described by Denning et al. (6). The unfavorable outcomes in these two patients may also have been influenced by the underlying immune dysfunction in these patients.

The variations in serum itraconazole concentrations observed in individual patients over time warrant discussion. Variations in concentrations during the initial 6 h following the morning dose and discrepancies between the 0- and 12-h concentrations are intriguing and difficult to explain. The study design and methods used did not allow a detailed pharmacokinetic analysis. Itraconazole undergoes extensive metabolism after absorption (36). A study comparing analytical methods reported consistently higher itraconazole concentrations in patient serum specimens when measured by bioassay methods than when measured by high-performance liquid chromatography (40). The lack of an observed discrepancy in comparisons of spiked serum samples by these methods supports the existence of a biologically active metabolite (40). It is likely that such metabolites could differ with regard to biological activity and pharmacokinetic properties. It is possible that such biologically active metabolites could act synergistically or antagonistically with respect to time and individual concentration, with the sum effect reflected in a single measurement by a bioassay. Sufficient time to allow for metabolic production might be required before these effects could be measured, resulting in the later detection of increases in concentrations by bioassay methods. Such a hypothesis could explain the late increases in itraconazole concentrations observed. The consistency in values measured in individual patients after 12 h was anticipated and supports the validity of the bioassay.
As described above, patients on long-term twice-daily dosing were admitted the evening prior to evaluation, with only the morning dose administered during the 24 h of pharmacokinetic analysis. Premedication compliance could not be assured. It is possible that some patients attempted to catch up on missed doses just prior to the scheduled admission or that dosing the evening prior was delayed by the admission process and that its effects were still peaking at the time of 0-h sampling.

In addition to its efficacy, itraconazole appears to be better tolerated than its predecessor, ketoconazole. In doses of up to 400 mg/day in the treatment of systemic mycoses, the overall incidence of adverse effects has been in the range of 4 to 10% (11). In the present study, gastrointestinal effects and hepatotoxicity were not noted. Hepatotoxicity with ketoconazole is uncommon and may not be dose related (13, 14, 18). Therefore, until further experience with itraconazole accumulates, a lack of serious hepatic effects should be interpreted cautiously.

Until the present report, adrenal suppression was not associated with itraconazole (24). The higher (600-mg) dose of itraconazole gave serum values above those previously reported for a dose of 400 mg/day (12). In studies with a dose of 400 mg/day, a dose and time dependency of the half-life values noted, with a markedly increased half-life at higher doses and after 2 weeks of treatment (12). The long half-life (>24 h) and resultant drug accumulation over 2 weeks may have accounted for the delayed onset of adrenal insufficiency in the patient.

Hypokalemia during treatment with itraconazole was noted in prior case reports of two patients and in a few patients in other studies (2, 8, 11). In the present study, there was a significant reduction in serum potassium values during treatment with itraconazole at 600 mg/day. The simultaneous occurrence of hypertension, edema, and hypokalemia during itraconazole treatment suggests the possibility of drug-induced Conn’s syndrome. Although the change in blood pressure did not reach statistical significance for the group, two patients did experience a significant increase.

Although not previously considered clinically relevant, in vitro studies with rat and bovine testes and adrenal glands and in vivo studies with rats have suggested an effect of high doses of itraconazole on steroidogenesis (36). In vivo studies with rats and high doses of itraconazole have demonstrated a slight decrease in progesterone synthesis, a more significant decrease in cortisol synthesis, and an increase in testosterone synthesis (36). Measurement of urinary adrenal metabolites in one of our patients (no. 8) showed normal levels of 17-ketosteroids, depressed levels of free cortisol, and depressed levels of 17-hydroxy corticosteroids. These data in humans thus support those in rats: a defect in cortisol synthesis but relatively normal synthesis of androgenic hormones.

Therefore, the endocrine system suppression seen with itraconazole is distinct from that produced by ketoconazole. Although further study will help elucidate the exact mechanism of itraconazole-induced hormone effects, our data are consistent with a greater sensitivity of the 11-β-hydroxylase to inhibition by itraconazole, with a relative sparing of the C17-20 lyase enzyme activity (androgen synthesis).

In general, the increased potency of itraconazole may allow for the use of lower doses of this drug than of other azoles. Short courses of treatment with 50 to 100 mg/day are effective in most superficial fungal infections. Responses have also been seen in some systemic mycotic infections (4, 21, 28, 32, 36). Adverse reactions at 50 to 100 mg/day are minimal. There is no evidence of endocrine system deficiencies during treatment with low doses given for relatively brief durations, and the effects irregularly seen at 600 mg/day should not deter physicians from using lower doses of itraconazole for less severe infections (4, 24).

In our limited experience, the toxicities described here appear to respond to standard intervention, such as potassium supplementation, diuretics, antihypertensive agents, and/or dose reduction. More frequent monitoring of potassium levels in serum may be warranted during treatment with higher doses or for prolonged durations.

The optimal dose for the treatment of severe systemic mycoses has yet to be determined. The present study suggests that selected patients with severe systemic mycoses might benefit from 600 mg of itraconazole per day. However, the risk/benefit ratio must be weighed as the dose-related improvement in efficacy is counterbalanced by dose-related adverse reactions.

ACKNOWLEDGMENTS

We thank Janssen Pharmaceutica for support. The Audie L. Murphy Veterans Hospital Special Diagnostic and Treatment unit was supported by NIH grant M01-RR-01346. The nursing and dietetic care provided by the staff at the Audie L. Murphy Veterans Hospital Special Diagnostic and Treatment unit is appreciated. We thank Charles J. Lerner, Charlotte Watson, Michael F. Luther, and the staff of the computer resource center at the Audie L. Murphy Veterans Hospital for assistance.

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