Adrenal Response to Corticotropin during Therapy with Itraconazole

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Itraconazole is a triazole with a mechanism of action similar to that of ketoconazole. Endocrine side effects of ketoconazole, including impaired cortisol synthesis, have been well documented (A. Pont, J. R. Graybill, P. C. Craven, J. N. Galgiani, W. E. Dismukes, R. E. Reitz, and D. A. Stevens, Arch. Intern. Med. 144:2150–2153, 1984). We examined the adrenal response to corticotropin in 10 patients being treated with itraconazole. No impairment of cortisol synthesis could be demonstrated.

Itraconazole (R 51,211) is a broad-spectrum oral antifungal agent currently undergoing clinical trials in both dermatophyte infections and the systemic mycoses. This compound shares structural similarities with the imidazole derivative ketoconazole (5). Furthermore, the drugs are believed to have similar mechanisms of action (19).

Ketoconazole was first recognized to have endocrine side effects when some patients receiving the drug developed gynecomastia (3). Further studies demonstrated interference of ketoconazole with androgen (6, 12, 14, 15), estrogen (10, 20), and glucocorticoid synthesis (9, 13). Studies of steroidogenesis in cultured mouse adrenal cortex tumor cells indicate that ketoconazole directly inhibits 11β-hydroxylase activity (7). There are only a few reports in which clinically significant hypoadrenalism has been attributed to ketoconazole therapy (17, 18, 21). The similarities between itraconazole and ketoconazole prompted us to study the adrenal response to corticotropin in patients receiving itraconazole therapy for a variety of mycotic infections.

Of 10 patients referred for therapy of documented mycotic infections, 6 had coccidioidomycosis and 1 each had mucocutaneous candidiasis, aspergilloma, cutaneous sporotrichosis, and pulmonary cryptococcosis. A brief clinical outline of the patients studied is presented in Table 1.

Several patients had received prior antifungal therapy, and five (patients no. 1, 2, 4, 6, and 7) had been treated with ketoconazole. None of the patients received concomitant antifungal agents during itraconazole therapy.

Three additional patients (one each with aspergilloma, pulmonary coccidioidomycosis, and disseminated coccidioidomycosis) who completed baseline adrenal testing before itraconazole therapy did not consent to follow-up corticotropin studies.

The 1-h corticotropin stimulation tests were performed as previously described (1). The 8-h tests were conducted with a continuous 8-h infusion of corticotropin (cosyntropin; 400 μg in 500 ml of 5% glucose in water). Patients receiving either 100 or 200 mg of itraconazole per day took a single daily dose with breakfast, whereas those receiving 400 mg/day took a divided dose of 200 mg twice daily with meals. We performed 8-h corticotropin tests from 8 a.m. to 4 p.m. in three patients (no. 2, 3, and 10) and from 4 p.m. to midnight in two patients (no. 1 and 5). Measurements of

cortisol in serum were made just before and 0.5, 1, 2, 4, and 8 h after the infusion was started. Cortisol measurements in serum were made by radioimmunoassay (Becton-Dickinson and Co.; ARIA-HT).

Patients were evaluated clinically at intervals of 1 or 2 months. Interviews included questioning regarding endocrine dysfunction, and physical examinations were performed with particular attention to progress of the fungal disease in addition to weight loss, hyperpigmentation, hypotension, and gynecomastia. Laboratory studies included electrolyte levels in serum, renal and hepatic functions, complete blood counts, and leukocyte differential counts. Concentrations of itraconazole in serum were measured by high-pressure liquid chromatography (Janssen, Beerse, Belgium) 1, 2, 4, 8, 12, 16, and 24 h after the morning dose.

Since enrollment in the study, the 10 patients (Table 1) were followed up for a mean of 11.4 months, with a range of 6 to 20 months. None demonstrated clinical or laboratory (hyponatremia, hyperkalemia, or eosinophilia) evidence of endocrine dysfunction.

The adrenal response to corticotropin in the control group (preitraconazole therapy) was assessed with the 1-h test in four patients and with the 8-h test in five patients before itraconazole treatment started. The results of the 1-h tests were normal as defined by a doubling of the cortisol level in serum or a rise to a level above 20 μg/dl. We are not aware of published data for the normal range of responses to 8-h corticotropin studies; however, marked rises in cortisol levels in serum were apparent in all instances, and the mean (±2 standard deviations) for the five pretreatment control studies defined our normal range.

The adrenal response to corticotropin of patients receiving itraconazole (100 mg/day) was measured with the 8-h test (patients no. 2, 4, 6, and 7) and the 1-h test (patient no. 8). The results were normal, not differing significantly from those of the control group. Patients treated with 200 mg of itraconazole per day had normal results when tested with the 8-h (patients no. 1 and 9) and 1-h (patient no. 7) corticotropin stimulation tests. Five patients (patient no. 1, 2, 3, 5, and 10) treated with 400 mg of itraconazole per day had 8-h corticotropin testing. All of these results were normal (Fig. 1) and did not differ significantly from those of the control group.

Itraconazole determinations in serum were available for 8 of the 10 patients. These measurements were not made on the same day as the corticotropin studies. For patients taking 400 mg of itraconazole per day, the range of peak concentrations was 2.25 to 2.42 μg/dl, and the range of concentrations 24 h after the dose was 1.75 to 2.42 μg/dl; among

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TABLE 1. Clinical outline and treatment of patients studied

Patient no.	Age (yr)/sex	Mycosis	Itraconazole dose (mg/day)	Duration RX[a]
1	24/Male	Disseminated coccidioido-mycosis	200 / 400	2 mo / 13 mo
2	32/Male	Disseminated coccidioido-mycosis	100 / 200 / 400	1 mo / 1 mo / 1 day
3	21/Male	Disseminated coccidioido-mycosis	400	5 mo
4	38/Male	Pulmonary coccidioido-mycosis	100	12 mo
5	29/Male	Pulmonary coccidioido-mycosis	400	1 mo
6	7/Male	Sporotrichoid coccidioido-mycosis	100	4 mo
7	26/Male	Chronic mucocutaneous candidiasis	100 / 200	2 mo / 5 mo
8	49/Male	Aspergilloma	100	2 wk
9	72/Male	Cutaneous sporotrichosis	200	8 mo
10	67/Female	Pulmonary cryptococcosis	400	1 mo

[a] Duration RX, Duration of therapy at that particular itraconazole dosage when corticotropin stimulation was performed.

patients taking 200 mg/day, the comparable values were 0.35 to 0.94 and 0.16 to 0.61 μg/dl, respectively; and among patients taking 100 mg of itraconazole per day, the comparable values were 0.14 to 0.74 and 0.18 to 0.29 μg/dl, respectively.

Itraconazole is potentially useful for the treatment of a number of dermatophyte and systemic mycotic infections (1st International Symposium on Itraconazole, October, 1985, Oaxaca, Mexico, Rev. Infect. Dis., in press). Keto-conazole has been shown to be an effective antifungal agent (4); however, its use may be attended by significant toxicity, the most notable being gastrointestinal, hepatic (8), and
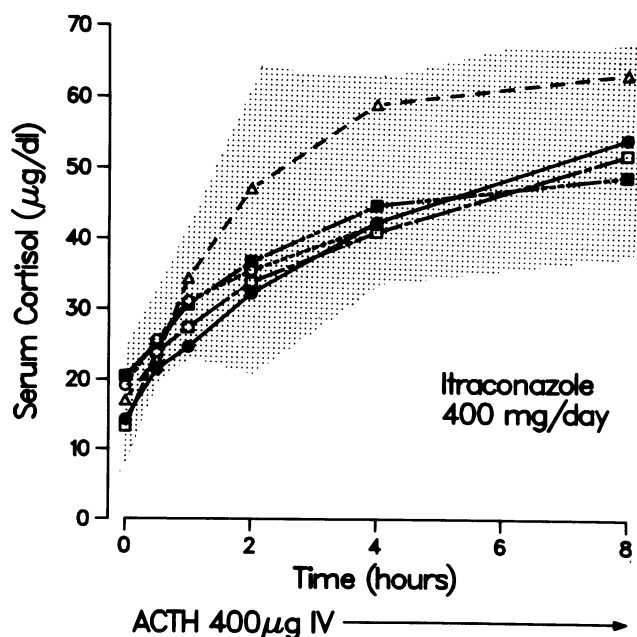

FIG. 1. Results of 8-h corticotropin stimulation testing in five patients treated with itraconazole (400 mg/day). The shaded area represents the normal range as defined by pretreatment controls.

endocrine (11). An increasing number of reports of adverse endocrine effects of ketoconazole being used to manage certain endocrinopathies and hormone-dependent neoplasia suggests that this imidazole derivative may prove to be more useful as an endocrine drug than as an antimicrobial agent (2, 16).

Despite the relatedness of these two drugs, the results of this study suggest that itraconazole does not share the adverse effect of ketoconazole upon glucocorticoid synthesis in humans treated with maximum doses (currently 400 mg/day) of itraconazole. Neither clinical nor laboratory evidence of hypoadrenalism could be demonstrated in any of the 10 cases evaluated. The patients of this study were followed up for a mean duration of 11.4 months of treatment, and 5 of the 10 were treated with the maximum dosage. These results are consistent with studies of cortisol and testosterone levels in the plasma of healthy volunteers (R. De Coster et al., Janssen Clinical Research Report, R 51211/2, 1983) and beagle dogs (R. De Coster, M. Michiels, and D. Beerens, Plasma Itraconazole, Testosterone and Cortisol Levels after Daily Oral Administration for 3 Months in Beagle Dogs [preclinical research report], Janssen Research Products Information Service, 1984).

Limited pharmacokinetic data are available for itra-conazole. The half-life is between 11 and 15 h in humans, and a 200-mg oral dose usually results in peak levels in serum of 0.2 to 0.3 μg/ml (R 51,211, basic medical information brochure, Janssen Pharmaceutica, 1983). Levels of itraconazole in serum measured by high-pressure liquid chromatography (Janssen, Beerse, Belgium) were available in 8 of the 10 cases. These results indicated adequate absorption of the drug and that in some instances levels were greater than anticipated for the dose administered.

None of the 10 patients in this study nor any of the other 21 we have enrolled in itraconazole protocols manifested clinical evidence of endocrine dysfunction. Testosterone levels were not measured in our patients, and the possibility of itraconazole-induced subclinical abnormalities of andro-gen biosynthesis cannot be excluded. One possible explana-tion for the apparent sparing of steroidogenesis by itraconazole is that its inhibition of cytochrome P-450-dependent enzymes is more selective for fungal than mam-malian cells, compared with the inhibition observed with other triazole and imidazole derivatives (G. Willemsens and H. Van den Bossche, Effect of Imidazole and Triazole Derivatives on Cytochrome P-450 in Yeast and Rat Liver Microsomes [research report], Janssen Research Products Information Service, 1982).

Although clinical experience with itraconazole is limited, to date there are no reports of significant endocrine toxicity. Further studies may be needed to evaluate androgen biosyn-thesis in itraconazole-treated patients.

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