Reversible Adrenal Insufficiency Induced by Ketoconazole

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KETOCONAZOLE, an imidazole antifungal drug, blocks testicular and adrenal steroid synthesis in a dose-dependent and time-dependent manner, presumably correlating with serum levels of ketoconazole.[1-5] Although hypogonadism and gynecomastia caused by ketoconazole have been reported, symptomatic hypoadrenalism has not yet been described,[1,4,6] to the best of our knowledge. We report a patient who developed symptoms and signs of hypoadrenalism while receiving an experimentally high daily dose of ketoconazole. The results of serum and urinary steroid measurements confirmed this clinical impression. All symptoms and signs of adrenal insufficiency resolved promptly following discontinuation of ketoconazole therapy.

Methods

A one-hour intravenous adrenocorticotropic hormone (ACTH) (cosyntropin [Cortrosyn]) test,[7] a 48-hour intravenous ACTH (Cortrosyn) test,[8] and a metyrapone (Metopirone) test[9] were performed during ketoconazole therapy and were repeated after its discontinuation.

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Read in part before the 83rd annual meeting of the American Society for Microbiology, New Orleans, March 9, 1983.

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Report of a Case

A hypertensive 48-year-old black man had an average blood pressure of 140/90 mm Hg with methyldopa (Aldomet), 500 mg/day, and a combination of triamterene, 50 mg, and hydrochlorothiazide, 25 mg (Dyazide), 2 capsules per day, and sodium restriction. He acquired pulmonary blastomycosis and was treated with ketoconazole (Nizoral), 800 mg orally at 6 AM daily on an experimental protocol. In the third week of this therapy, he developed emotional lability, depression, generalized weakness, malaise, anorexia, and orthostatic dizziness. He also noted that for the first time in his life he had a suntan. He denied abdominal pain or other gastrointestinal complaints.

Physical examination revealed relative hypotension with blood pressures measured as low as 100/60 mm Hg. There was hyperpigmentation of the anterior thighs, with a "suntan line" where the edge of his shorts had been. There was no other hyperpigmentation. His weight was constant. Although he had mild hyponatremia (serum sodium level, 132 to 136 mEq/L) throughout therapy, this was not different from his serum sodium concentrations before or after the period of ketoconazole therapy. Neither gynecomastia, hyperkalemia, hypoglycemia, nor eosinophilia developed.

After discontinuation of both methyldopa and sodium restriction and after reduction of the triamterene/hydrochlorothiazide dose to 1 capsule per day, his blood pressure averaged 125/70 mm Hg for the duration of the course of ketoconazole. Coincident with peak serum ketoconazole levels on day 32, a morning plasma cortisol level was low and a one-hour ACTH test result was abnormal, supporting a diagnosis of adrenal insufficiency (Table).

During a 48-hour ACTH test on days 41 through 43 and during a metyrapone test on days 173 through 175, 17-hydroxysteroid excretion was low, but measurements of urinary free cortisol and tetrahydrodeoxycortisol levels, respectively, demonstrated adrenal reserve (Table). Because his symptoms improved during continued ketoconazole therapy and because he had early morning cortisol levels of 11 and 14 μg/dL coincident with trough ketoconazole concentrations (Table), he did not receive glucocorticoid therapy. The mean of 12 peak ketoconazole serum levels determined two hours after daily oral doses was 11.3 μg/mL. His pulmonary infiltrates cleared completely, and ketoconazole therapy was discontinued after 187 days of treatment. Within days, his symptoms completely resolved, and his blood pressure rose to 160/100 mm Hg. The same antihypertensive regimen that he had followed prior to ketoconazole therapy stabilized his blood pressure at 140/95 mm Hg. On days 38, 46 through 48, and 54 through 56 after ketoconazole therapy was stopped, one-hour ACTH, 48-hour ACTH, and metyrapone tests were normal, respectively (Table).

Comment

Since discontinuation of ketoconazole therapy led to prompt resolution of symptoms and signs of hypoadrenalism, and since pituitary-adrenal function was then proven to be normal, ketoconazole and not blastomycotic adrenalitis was the likely cause of the adrenal insufficiency demonstrated in our patient. Lack of intercurrent illness, treatment with a potassium-sparing diuretic, or unknown effects of ketoconazole on aldosterone synthesis may account for the absence of hyponatremia and

Tests of Pituitary-Adrenal Function							
		With Ketoconazole Therapy			Without Ketoconazole Therapy		
	Normal Values	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1-hr Adrenocorticotropic hormone test							
Plasma cortisol (morning), μg/dL							
Time 0	6-20	4*	...	...	13	...	...
At 1 hr	6-20	5*	...	...	33	...	...
48-hr Adrenocorticotropic hormone infusion test							
Plasma cortisol (morning), μg/dL	6-20	11†		38	24		67
Urinary steroids (24 hr)							
17-Hydroxysteroids, mg/g of creatinine	3-7	1.6	13	18.2	3.7	21.8	34.9
Free cortisol, μg	20-90	19	567	801	45	2,250	2,600
Tetrahydrodeoxycortisol, mg	<1	0.9	6.5	12	1	9	13
Metyrapone test							
Plasma cortisol (morning), μg/dL	6-20	14†		19	15		45
Plasma adrenocorticotropic hormone (morning), pg/mL	0-120	70†		550	15		390
Urinary steroids (24 hr)							
17-Hydroxysteroids, mg/g of creatinine	3-7	2.9	3.3	6.7	4.1	5.8	11.7
Free cortisol, μg	20-90	25	11	11	66	28	20
Tetrahydrodeoxycortisol, mg	<1	1.2	3.7	10.6	1	7.4	22

*Coincident with peak serum ketoconazole concentration.
†Coincident with trough serum ketoconazole concentration.

hyperkalemia typical of adrenocortical failure.

The experimentally high dose of ketoconazole used in our patient may explain the lack of more widely recognized hypoadrenalism from ketoconazole in usual practice, where doses and serum levels are lower. Also, because the usual morning dosing of ketoconazole results in peak serum levels after maximal diurnal cortisol production has occurred during the early morning hours, more profound hypoadrenalism with addisonian crisis is perhaps avoided. Symptoms of hypoadrenalism have not been detected in prospective studies of patients treated with similarly high doses of ketoconazole.[3] However, there may be variation among individuals in their susceptibility to these effects, and Pont et al[3] suggest that patients taking high doses of ketoconazole be considered at risk for symptomatic adrenal insufficiency. Interestingly, there may have been physiologic compensation for the hypoadrenalism in our patient as indicated by the spontaneous clinical improvement and by the trend toward higher values of serum cortisol and urinary steroid excretion with continued ketoconazole therapy (Table). Although Pont et al[3] noted a possible partial reversal of suppression of testosterone secretion with more prolonged ketoconazole therapy, they did not find a correlation of duration of ketoconazole and its degree of suppression of adrenal steroidogenesis.

In vitro, ketoconazole inhibits adrenal P450-dependent mitochondrial enzymes performing cholesterol side-chain cleavage and 11-β-hydroxylation.[10,11] Comparison of the 17-hydroxysteroid and tetrahydrodeoxycortisol excretion while the patient was receiving ketoconazole and later while not taking ketoconazole during metyrapone testing (Table) suggests that metyraponelike inhibition of 11-β-hydroxylase is not the primary site of ketoconazole's interference in cortisol synthesis. Rather, ketoconazole seems to exert its principal inhibitory effect at an earlier step in the biosynthetic pathway. That the ability of ketoconazole to inhibit adrenal steroid synthesis is additive with the effect of metyrapone is supported by our finding that the ACTH levels were much higher before and after metyrapone testing while the patient was taking ketoconazole than when he was not taking ketoconazole.

In summary, ketoconazole administered in experimentally high doses resulting in high serum levels can inhibit adrenal steroidogenesis, which rarely may cause clinically apparent hypoadrenalism. This inhibitory effect may be partially overcome by endogenous compensatory mechanisms and is totally reversible with discontinuation of ketoconazole therapy.

Ketoconazole was supplied free of charge by Janssen Pharmaceutica Inc, Piscataway, NJ.

The authors acknowledge Barbara G. McCord, who prepared the manuscript, and David N. Orth, MD, who provided valuable advice on the laboratory evaluation of pituitary-adrenal function. We extend special thanks to Lawrence K. Wolfe, MD, for his critique of the manuscript.

This patient was treated under the National Institutes of Health–National Institute of Allergy and Infectious Diseases Mycoses Study Group Phase III Study on ketoconazole in the therapy of histoplasmosis and blastomycosis.

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