**Case Report**

**Preoperative ketoconazole therapy for adrenocortical carcinoma**

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Ketoconazole, an imidazole derivative, is a broad-spectrum antifungal agent. The development of gynecomastia in some men receiving ketoconazole fostered research into the drug's inhibitory effects on the production of testosterone and, subsequently, other steroid hormones. Ketoconazole has been used in the treatment of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome (Cushing's disease and ectopic ACTH syndromes), but there has been little experience with its use in Cushing's syndrome of primary adrenal origin.

We report a case of adrenocortical carcinoma in which preoperative ketoconazole therapy resulted in short-term clinical improvement.

**Case report**

A 60-year-old woman with a 4-month history of hypertension presented to hospital comatose. The hypertension had been treated with a diuretic and prazosin until 2 days before presentation, when hydralazine was substituted. The blood pressure on admission was 230/130 mm Hg and the pulse rate was 80 beats/min. No focal neurologic abnormalities were detected. Initial laboratory investigation revealed mild hyponatremia (serum sodium level 129 mmol/L) and respiratory alkalosis. Toxicology test results were negative.

The hypertension responded to intravenous hydralazine therapy. The patient resisted opening of her eyes but was otherwise unresponsive. Computed tomography (CT) of the head revealed normal findings. Episodes of catatonic behaviour occurred, and haloperidol therapy was started because of suspected hysteria.

By the third hospital day the patient was conscious and related a 2-month history of easy bruising, thin skin, hirsutism, facial plethora and puffiness, and muscle weakness. Her blood pressure was 120/75 mm Hg after antihypertensive therapy was stopped. Subsequently it increased to 210/120 mm Hg, and prazosin, 6 mg/d, was given.

The catecholamine levels in a 24-hour urine collection were normal before prazosin therapy was started. The serum cortisol level was 790 (normally 170 to 580) nmol/L at 8 am and 849 (normally 50 to 300) nmol/L at 4 pm. The serum aldosterone level was 598 (normally 80 to 280) pmol/L at 8 am. The plasma level of ACTH was 9 (normally less than 22) pmol/L, of testosterone 6.7 (normally less than 2.3) nmol/L, and of dehydroepiandrosterone sulfate (DHEA-S) 18 (normally less than 1.7) μmol/L. The urine level of 17-ketosteroids was 250 (normally less than 52) μmol/d. The free cortisol level in a 24-hour collection of urine was markedly elevated, did not respond to low-dose dexamethasone administration and failed to decrease by 50% or more with high-dose dexamethasone administration (Fig. 1). The plasma cortisol levels at 4 pm on the second day of low-dose and high-dose dexamethasone administration were 850 and 687 nmol/L respectively.

Ultrasonography revealed a solid mass 9 × 5 × 7 cm in the left adrenal gland; CT showed a well-defined encapsulated mass with radiolucent areas. The liver appeared normal. Bone scanning revealed increased uptake in the third, fourth and fifth ribs on the left side, and X-ray films confirmed the presence of rib fractures.

Adrenocortical carcinoma was suspected on the basis of a large adrenal mass, rapidly progressive signs and symptoms, and biochemical evidence of increased secretion of androgens (testosterone, DHEA-S and 17-ketosteroids), cortisol and aldosterone. In preparation for surgery the patient was given ketoconazole, the dosage being gradually increased from 200 mg once daily to 200 mg three times daily. The free cortisol level in a

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24-hour collection of urine returned to normal (Fig. 1). The blood pressure was normal after the withdrawal of prazosin therapy, and the plethora was alleviated.

Twelve days after the institution of ketoconazole therapy the tumour was resected under glucocorticoid coverage, with incidental splenectomy. No metastases were noted. The tumour weighed 291 g and measured 14 × 8 × 6 cm. Histologic study confirmed the clinical diagnosis of adrenocortical carcinoma and revealed vascular invasion and areas of hemorrhage and necrosis. After surgery the plasma levels of aldosterone, testosterone and androstenedione and the urine level of 17-ketosteroids were normal with the use of dexamethasone, 1 mg/d. Ketoconazole therapy was stopped.

Three months after surgery the patient presented with a recurrence of her original symptoms. The free cortisol level in a 24-hour collection of urine was again markedly elevated, and hepatic metastases were present. Mitotane therapy was ineffective, and she died shortly thereafter.

Comments

Ketoconazole has been shown to be a potent inhibitor of mitochondrial enzymes of the cytochrome P450 system. In healthy male volunteers a single 600-mg dose given orally resulted in a statistically significant reduction in testosterone levels for up to 8 hours. Higher doses, 800 to 1200 mg/d, resulted in persistently low testosterone levels in some patients. This effect is thought to be due to inhibition of the 17-20 lyase enzyme. In addition, gynecomastia, decreased libido, impotence and oligospermia have been noted. Another study demonstrated a reduction in 1,25-dihydroxyvitamin D₃ levels in male volunteers receiving ketoconazole, 600 to 1200 mg/d, for 1 week.

In vitro studies have suggested several actions of ketoconazole within the adrenal gland; these include (a) inhibition of desmolase activity in the side-chain cleavage of cholesterol to pregnenolone, (b) inhibition of 11-hydroxylation catalysis of deoxycorticosterone to corticosterone and of 18-hydroxydeoxycorticosterone to 18-hydroxycorticosterone and (c) inhibition of 18-hydroxylase catalysis of deoxycorticosterone to 18-hydroxydeoxycorticosterone and of corticosterone to 18-hydroxycorticosterone. Studies involving isolated rat adrenal cells demonstrated no inhibition by ketoconazole of noncytochrome P450 enzymes.

Ketoconazole has been used as primary or adjunctive treatment in patients with ACTH-dependent Cushing’s syndrome (Cushing’s disease) before or after transsphenoidal pituitary surgery and in those with metastatic small cell carcinoma of the lung associated with ectopic ACTH production.

In addition, ketoconazole has been used to treat benign and malignant adrenal tumours. Contreras and associates reported a case in which a 21-year-old woman with an adrenal rest tumour of the liver causing Cushing’s syndrome was treated for 42 days preoperatively with ketoconazole, up to 1000 mg/d. In another case a patient with adrenal carcinoma and metastases in the liver and lungs responded to treatment with ketoconazole, 1200 mg/d, with an apparent reduction in the size of the metastases. Oeklers and colleagues reported on the effects of ketoconazole on adrenocortical micronodular adenomatosis in vivo and in vitro.

The case we have described demonstrates the clinical effectiveness of short-term preoperative ketoconazole treatment in Cushing’s syndrome due to adrenocortical carcinoma. Although acute adrenal insufficiency has been associated with ketoconazole therapy, it did not develop in this patient. Ketoconazole appears to be useful as adjunctive therapy for the many causes of increased production of adrenal steroid hormones.

References


Fig. 1 — Effect of dexamethasone administration and ketoconazole therapy on urinary free cortisol level (urinary free cortisol excretion in 24 hours, corrected for creatinine clearance) in patient with adrenocortical carcinoma. Solid horizontal line represents upper limit of normal, based on creatinine clearance of 135 L/d and urinary free cortisol excretion of 300 nmol/d.

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