Non-suppression of cortisol secretion by long term treatment with ketoconazole in patients with acute leukaemia

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SUMMARY Ketoconazole, a potent antifungal agent, inhibits adrenal steroidogenesis in normal subjects during short term treatment. Since this drug is used in the long term prophylaxis of fungal infections in patients with haematological malignancies, we have investigated whether such patients have evidence of adrenocortical suppression. Six patients on long term prophylaxis with ketoconazole were given tetracosactrin stimulation tests. All patients had high basal cortisol concentrations, which increased further after administration of 25 IU of tetracosactrin. It is concluded that leukaemic patients receiving long term ketoconazole treatment do not have adrenocortical suppression. They may, in fact, have hyperstimulated adrenocortical function due to stress and hypovolaemia.

Ketoconazole is a potent antifungal agent which is used both for treatment of established fungal infections¹ and for long term prophylaxis of such infections in immunocompromised patients.² One major class of patients treated with this drug consists of those with acute leukaemia,² who are treated with chemotherapeutic agents and total body irradiation. In view of the reports that this drug suppresses steroidogenesis by the adrenal gland³ and testes⁴ in normal subjects, we investigated the possibility that patients with acute leukaemia treated with this drug may have a progressive reduction in adrenal steroidogenesis and may therefore be vulnerable to addisonian crisis.

Patients and methods

Six patients undergoing treatment with ketoconazole were included in this study; three patients had acute myeloblastic leukaemia, two had acute lymphoblastic leukaemia, and one had a non-Hodgkin's lymphoma. They were aged between 24 and 68 years (median 33 years). These patients were being treated with a variety of chemotherapeutic agents. Two patients had been given bone marrow transplants, but had had no overt gastrointestinal symptoms such as diarrhoea. The patients had

been receiving ketoconazole (400 mg daily) for between two and six weeks (median four and a half weeks).

A 24 h collection of urine was carried out for each patient for the measurement of urinary free cortisol. In addition, a short corticotrophin (Synacthen, Ciba) stimulation test was also carried out on all the patients: 25 IU of adrenocorticotrophin was injected after the collection of a venous blood sample in a heparinised glass tube. A second venous blood sample was collected 30 min later. The blood samples were centrifuged and the plasma was separated and frozen. Cortisol was measured in plasma and urine samples by a specific radioimmunoassay using a double antibody technique. All stimulation tests were carried out within 4 h of the last dose of ketoconazole.

Results

In three of the six patients 24 h urinary free cortisol secretion was greater than normal, while the remaining three had cortisol excretions within the normal range (Table). Basal plasma cortisol concentration was higher than normal in five of the six patients, and in one it was in the high normal range. After stimulation with adrenocorticotrophin the concentration of cortisol increased further; in all cases it

Urinary free cortisol excretion and plasma cortisol concentrations before and after corticotrophin administration

Patient no	Urinary free cortisol excretion* (nmol/24 h)	Plasma cortisol concentration (mmol/l)	
		Before corticotrophin†	After corticotrophin‡
1	612	658	1112
2	154	550	730
3	269	350	440
4	312	670	890
5	418	784	984
6	202	712	916

*Normal range 150 to 350 nmol/24 h.

†Normal plasma cortisol range 200 to 650 nmol/l.

‡After administration of Synacthen, cortisol must increase to 550 nmol/l or more.

was greater than 550 mmol/l, the value considered to be normal in our laboratory. In none of the patients was either urinary free cortisol excretion or plasma concentration of cortisol below normal.

In three of the six patients urinary free cortisol and plasma cortisol (9.00 am) measurements were also carried out before ketoconazole treatment. The urinary free cortisol excretion and plasma cortisol concentration were within the normal range in all three.

Discussion

These results show that leukaemic patients treated with ketoconazole in the long term do not have impaired cortisol secretion; this is borne out by both urinary excretion and plasma concentrations of cortisol before and after stimulation with corticotrophin. Since all stimulation tests were performed about 4 h after administration of ketoconazole, the possibility that the tests were carried out when plasma concentrations of this drug were low is unlikely. Furthermore, any significant, consistent decrease in cortisol secretion by the adrenal gland would have resulted in a reduction of urinary free cortisol.

Two of the patients included in this study had received bone marrow transplants. These patients develop graft versus host disease of their small intestine; this results in impaired absorption of ketoconazole and thus leads to erratic concentrations of this drug in plasma.⁵ These two patients, however, had no overt diarrhoea or malabsorption. Furthermore, the various indices of cortisol secretion in them were no different from those in other leukaemic patients who had not had bone marrow transplants. Clearly, therefore, ketoconazole is a relatively safe drug as far as adrenocortical suppression in leukaemic patients is concerned. The theoretical risk of adrenocortical suppression hitherto shown in normal subjects has not been seen in patients with acute leukaemia. In fact, the presence

of supranormal urinary free cortisol and basal plasma concentrations raises the possibility that the adrenal cortex in these patients is probably under a state of hyperstimulation. This may be secondary to the stress of their illness and also to marginal hypovolaemia due to hypoalbuminaemia, from which these patients often suffer. Needless to say, under such circumstances their requirement of cortisol is probably greater than normal. These data are also relevant to the use of this drug in other cases such as prostatic carcinoma, where total inhibition of testicular steroidogenesis is required. The doses of ketoconazole required for such inhibition (up to 1600 mg daily) are much higher than those required for fungal infections, however, and would therefore pose a greater risk to adrenal steroid synthesis as well.⁶ Further investigation will be necessary to assess the safety of this drug in patients with prostatic carcinoma.

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