Effects of single and multiple doses of ketoconazole on adrenal function in normal subjects

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The plasma cortisol response to 0.25 mg tetracosactrin given by intramuscular injection was suppressed by nine oral doses of 200 mg ketoconazole given 12 hourly to nine normal female subjects. No effect was noted following a single 200 mg oral dose of ketoconazole. This suppressive effect was reversible within at least 5 days of discontinuation of ketoconazole.

Keywords ketoconazole plasmacortisol

Introduction

Ketoconazole is now established as an orally available antimycotic agent active against both superficial and deep infections by a broad spectrum of fungi. It is a potent inhibitor of testicular and adrenal steroid synthesis and blocks various cytochrome P450-linked enzyme systems (Santen *et al.*, 1983; Loose *et al.*, 1983). It is also has a hypocholesterolaemic action, mainly by inhibition of 14 α and possibly 4 α demethylation of lanosterol and rearrangement of the double bonds (Miettinen & Valtonen, 1984). Recently the anti-androgenic effect has been used in therapy for advanced prostate cancer (Trachtenberg & Pont, 1984). A recent report (Pont *et al.*, 1984) has shown that high dose ketoconazole (800–1200 mg day⁻¹) given for periods of less than 1 week to 18 months can produce gynaecomastia, oligospermia, azoospermia, impotence and reduced libido. In addition the urinary cortisol excretion was reduced and there was a depressed response to corticotrophin. In this short report we present the results of a study of adrenal responsiveness to corticotrophin following a single 200 mg dose and after a short course of ketoconazole given in the low doses advised for uncomplicated vaginal candidosis.

Methods

Ten healthy female volunteers mean age 24.7 years (range 19–32 years) and mean body weight 56.4 kg (range 49–66 kg) gave written informed consent to take part in the study, the protocol of which was approved by the Ethics Committee of Guy's Hospital Medical School. Subjects were ascertained to be normal by clinical and laboratory examination: a pregnancy test on an early morning specimen of urine was carried out within 5 days preceding the start of the study.

Ketoconazole was administered in a dose of 200 mg, 12 hourly for 5 consecutive days, each dose taken with a meal. Tetracosactrin (Synacthen) challenge tests were carried out 5 days before the start of drug administration (Day -5), after the first tablet of ketoconazole (Day 0), after the last tablet of the 5 day course (Day +5), and 5 days after completion of the course (Day +10). The Synacthen challenge tests were carried out between 10.30 h and 11.00 h, which was approximately 2 h after the morning ketoconazole dose.

Ketoconazole was supplied in the form of 200 mg tablets (Nizoral) from Janssen Pharmaceutical Ltd (Marlow, Bucks). The tetracosactrin used was Synacthen (Ciba-Geigy, Horsham, Sussex) and was prepared in the form of 0.25 mg

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tetracosactrin ml^{-1} . Synacthen (0.25 mg) was administered intramuscularly into the upper outer quadrant of the buttock. Synacthen tests were conducted after insertion of a butterfly (21 G; Abbott) needle into a forearm vein of the non-dominant arm followed by a period of approximately 30 min rest. Heparinised saline was used to maintain patency of the needle. Whole blood samples (5 ml) were taken before Synacthen administration and at 20, 30, 45, 60, 90 and 120 min after its injection for plasma cortisol estimations by radioimmunoassay (Amersham-RIA kit). The samples were gently transferred to lithium heparin tubes, centrifuged and the plasma removed and stored at -20°C until analysis.

Three measures of the effect of ketoconazole on the endogenous cortisol response to tetracosactrin (Synacthen) challenge were examined:

- (i) baseline plasma cortisol concentrations before tetracosactrin injection;
- (ii) maximum plasma cortisol concentration; and
- (iii) area under the plasma cortisol concentration, time profile (AUC) following tetracosactrin injection after subtraction of baseline plasma cortisol concentration.

These data were examined by two-way analysis of variance for treatment effect and significance of the difference between the means (two-tailed) of the variates were determined by the Student-Newman-Keuls procedure. Conclusions regarding treatment effects were checked by the non-parametric Friedman two-way analysis of

variance: in no case were the conclusions altered by use of a distribution-free method.

Results

The results from nine of the 10 volunteers were available for analysis. One subject withdrew from the trial after the initial dose of ketoconazole because of nausea and vomiting. Another subject experienced mild nausea during the 5 days of drug administration but completed the study.

Table 1 summarises the results of the cortisol measurements before, during and after discontinuation of ketoconazole administration. There was no significant difference between the baseline cortisol concentrations at any time during the study. A single 200 mg dose of ketoconazole (Day 0) produced no significant effect on the maximum plasma cortisol response to tetracosactrin but this was significantly depressed in all subjects by day +5 of ketoconazole treatment although day +10 showed a return to baseline values. The AUC (0–120 min) showed a similar pattern of behaviour and although there was a significant ($0.05 > P > 0.025$) difference between day +10 and day 0 values there was no difference between day +10 and day –5. In most cases the plasma cortisol concentration-time profile was substantially incomplete at 120 min and extrapolation of the data to infinite time was not appropriate. An alternative, although less likely explanation of this data might be that ketoconazole does not alter total AUC, but merely flattens and extends the response.

Table 1 Baseline plasma cortisol concentrations and maximum plasma cortisol concentration and area under the plasma concentration-time profile of the response following 0.25 mg tetracosactrin in nine subjects 5 days before (Day –5) and after a single 200 mg dose (Day 0) or 9×200 mg doses (Day +5) of ketoconazole. Day +10 studies were conducted 5 days after discontinuation of ketoconazole.

		<i>Time of study</i>			
		<i>Day –5</i>	<i>Day 0</i>	<i>Day +5</i>	<i>Day +10</i>
Baseline plasma cortisol concentration ($\mu\text{mol l}^{-1}$)	Mean	849	904	1094	819
	s.d.	267	273	395	312
	Median	920	960	1100	780
Maximum plasma cortisol concentration ($\mu\text{mol l}^{-1}$)	Mean	966	724	335*	1087
	s.d.	301	283	144	252
	Median	1050	870	350	1140
AUC (0–120 min) of plasma cortisol response ($\mu\text{mol l}^{-1} \text{ min}$)	Mean	74.1	51.7	15.2*	80.6
	s.d.	31.2	31.8	14.8	24.1
	Median	70.2	65.7	24.2	82.8

* $P < 0.001$ vs days –5, 0, +10

Discussion

There is now ample evidence that ketoconazole can affect steroid synthesis although the dose at which this has been previously demonstrated appears to be relatively high in comparison with doses usually used for uncomplicated candida infections and prophylaxis (Pont *et al.*, 1984). Dosage could well be an important factor since there is evidence of dose-dependant kinetics for ketoconazole (Daneshmend & Warnock, 1983) and thus the potential exists for non-linear accumulation of drug with increasing dose and disproportionate effects on steroid synthesis. Preliminary data suggests that plasma cortisol concentrations may be greatly depressed throughout the day in occasional patients taking high doses of ketoconazole (Pont *et al.*, 1983)

although only one case has been reported of a patient receiving ketoconazole manifesting hypoadrenalism (discussed by Pont *et al.*, 1984). This present data indicates that some degree of impairment of adrenal response may occur at ordinary clinical doses of ketoconazole. This effect is reversible within at least 5 days of discontinuation of ketoconazole confirming the observations of Pont *et al.*, (1984).

The clinical importance of our results is presently obscure although they could be of relevance where ketoconazole is administered to septicæmic and/or immunosuppressed patients as part of treatment or prophylaxis for infections.

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