Acta Endocrinologica (Copenh) 1987, 115: 265–271

Effects of high-dose ketoconazole and dexamethasone on ACTH-stimulated adrenal steroidogenesis in orchiectomized prostatic cancer patients

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Abstract. The effects of high-dose ketoconazole (i.e. 400 mg every 8 h) therapy on adrenal steroidogenesis were investigated in 7 patients with advanced prostatic cancer who no longer responded to orchiectomy. An ACTH challenge was performed before and on days 14 and 28 of high-dose ketoconazole treatment. During the last 14 days, dexamethasone (0.5 mg twice daily) was administered together with ketoconazole. High-dose ketoconazole alone lowered the basal levels of the androgens by 49–66%. It almost completely inhibited their stimulation by ACTH, whereas plasma progesterone was doubled. Basal cortisol was only slightly lowered, but the response to ACTH stimulation was markedly blunted. Basal and stimulated plasma aldosterone remained unaffected. Both basal and stimulated 11-deoxycortisol, 11-deoxycorticosterone, and, to a lesser extent, corticosterone rose more markedly after ketoconazole than after placebo. The basal and stimulated plasma adrenal androgen levels were further reduced after combined ketoconazole-dexamethasone treatment, whereas plasma corticosterone, 11-deoxycortisol, and 11-deoxycorticosterone were lowered in the same way as cortisol. Aldosterone and progesterone profiles were similar to those observed under high-dose ketoconazole, but plasma 17α-hydroxyprogesterone increased more markedly than after high-dose ketoconazole alone. These results demonstrate that high-dose ketoconazole lowers plasma androgen levels in orchiectomized patients and partly inhibits the gluco- and mineralocorticoid syntheses, especially after ACTH-stimulation. The addition of dexamethasone does not only correct the possible consequence of the impairment of the cortisol production by high-dose ketoconazole, but it further reduces the androgen levels and lowers the plasma concentrations of most precursors, for instance 11-deoxycorticosterone, which has some physiological mineralocorticoid activity. Therefore, a systematic combined therapy may be recommended, when high-dose ketoconazole treatment is given to patients with metastatic prostate cancer.

Ketoconazole is an oral active broad-spectrum antimycotic agent (Levine 1982). Its antifungal properties are due to the blockade of the cytochrome P-450 dependent 14-demethylase, catalyzing the synthesis of ergosterol in yeast and fungi (Vanden Bossche 1985). At higher doses, ketoconazole also inhibits the 17,20-lyase, a key enzyme of the androgen biosynthesis in the testes and adrenals and, to a lesser extent, the 11-hydroxylase and cholesterol side-chain cleavage enzymes of the adrenal gluco- and mineralocorticoid biosynthesis (Loose et al. 1983; Santen et al. 1983; Pont et al. 1984; Vanden Bossche et al. 1985, 1987; De Coster et al. 1986). When given to prostatic cancer patients at a high dose (i.e. 400 mg every 8 h), the plasma levels of ketoconazole are maintained above 4 mg/l and a sustained inhibition of both testicular and adrenal androgen production is achieved (Trachtenberg 1984; Heyns et al. 1985).

The interference of ketoconazole with the gluco- and mineralocorticoid pathways has been related to some impairment of the adrenal function in a few patients (Trachtenberg & Pont 1984;

White & Kendall-Taylor 1985; Denis et al. 1985; Tapazoglou et al. 1986).

Therefore it may appear advisable systematically to combine high-dose ketoconazole with a glucocorticoid substitution therapy. The present study was undertaken to investigate the effects of ACTH-challenges on the plasma levels of the main adrenal androgens, gluco- and mineralocorticoids, during high-dose ketoconazole or combined ketoconazole-dexamethasone treatment in patients with metastatic prostate cancer no longer responsive to orchiectomy. This unique patient group allowed us to study the effect of the drug on the adrenal steroids in a pure state uncontaminated by testicular steroids.

Patients and Methods

Patients and study design

Seven patients (mean age 68 years, range 54–80, mean weight 69 kg, 63–80) with histologically confirmed metastatic prostate carcinoma were included in this study. They had all undergone bilateral orchiectomy 16 to 81 months (mean 22 months) before, but had recently relapsed. Informed consent was obtained in writing and the investigation had been approved by the responsible Ethical Committee. During at least 28 days, they were treated with high-dose ketoconazole (400 mg every 8 h). The last 14 days, dexamethasone (0.5 mg twice daily) was added. Before the onset of treatment (day 0) and on days 14 and 28, a 60-min infusion of 0.25 mg of $ACTH_{1-24}$ (Synacthen, Ciba, Basel) was administered iv between 08.00 and 10.00 h. Plasma samples were taken 20 min before and 30, 60, 90, 120, 180 and 240 min after onset of the infusion.

Blood was collected in heparinized tubes, centrifuged immediately, and the plasma stored at −20°C.

The drug was well tolerated. Gastrointestinal upsets were observed in 3 patients and caused one of them to drop out after 16 days. The clinical characteristics of the patients included in this study have been published separately in abstract from (Denis et al. 1986) and will be described in detail in another study (Denis et al., in press).

Hormone assays

Plasma testosterone, androstenedione, dehydroepiandrosterone (DHEA), 17α-hydroxyprogesterone, and progesterone were assayed by radioimmunological methods as described in detail elsewhere (De Coster et al. 1984, 1986). Plasma aldosterone, cortisol, and dehydroepiandrosterone sulphate (DHEAS) were determined by direct assays using iodinated tracer and solid-phase antibodies. These commercial kits were purchased from Cis-Sorin (Gif-sur-Yvette, France), Becton-Dickinson Immunodiagnostics (New York, USA), and Cambridge Medical Diagnostics (Billerica, USA), respectively. The main cross-reacting steroids were: for the aldosterone antibody, corticosterone (0.006%), 18-hydroxycorticosterone (0.002%), and 11-deoxycorticosterone (DOC) (0.002%); for the cortisol antibody, 11-deoxycortisol (3.5%), and 17α-hydroxyprogesterone (0.17%); for the DHEAS antibody, DHEA (41%), androsterone (7.3%), and androstenedione (2.9%). The cross-reaction of ketoconazole and dexamethasone in these assays was at least lower than 0.08%.

Plasma corticosterone, DOC, and 11-deoxycortisol were measured after extraction and separation by high-pressure liquid chromatography (HPLC) as described earlier (De Coster et al. 1986).

Ketoconazole concentrations were determined by HPLC in most of the samples obtained before synacthen infusion (Woestenborghs et al. 1980).

Statistical analysis

For the dynamic tests, the area under the curve were computed by means of the trapezoidal rule. Wilcoxon's matched-paired, signed-ranks tests (two-tailed) were used for statistical analysis with statistical significance defined as $\leqq 0.05$.

Results

High-dose ketoconazole monotherapy lowered the basal plasma concentration of testosterone (T), androstenedione (Δ4), DHEA and DHEAS to, respectively, 47% ($P = 0.01$), 40% ($P < 0.01$), 34% ($P = 0.03$), and 51% ($P = 0.03$) of their control levels (Fig. 1). The rise of adrenal androgens observed in control ACTH-challenges, was reduced by ketoconazole for Δ4 ($P = 0.05$) and DHEA ($P = 0.01$). The area under the curve was also lowered for testosterone, from 256 ± 27 to 153 ± 34 nmol × l^{-1} × h^{-1} (mean ± SEM), but the level of significance was not reached. DHEAS did not change after ACTH stimulation.

The combined ketoconazole-dexamethasone treatment also lowered both basal concentrations (T to 44%, Δ4 to 14%, DHEA to 15%, and DHEAS to 10% of their control values, $P \leqq 0.05$) and ACTH-stimulated plasma androgen concentrations ($P = 0.03$, Fig. 1). Most of the values observed during combined therapy were lower than after ketoconazole alone, but the difference between the two therapies was only significant for DHEAS ($P = 0.03$).

The increment of plasma cortisol after ACTH

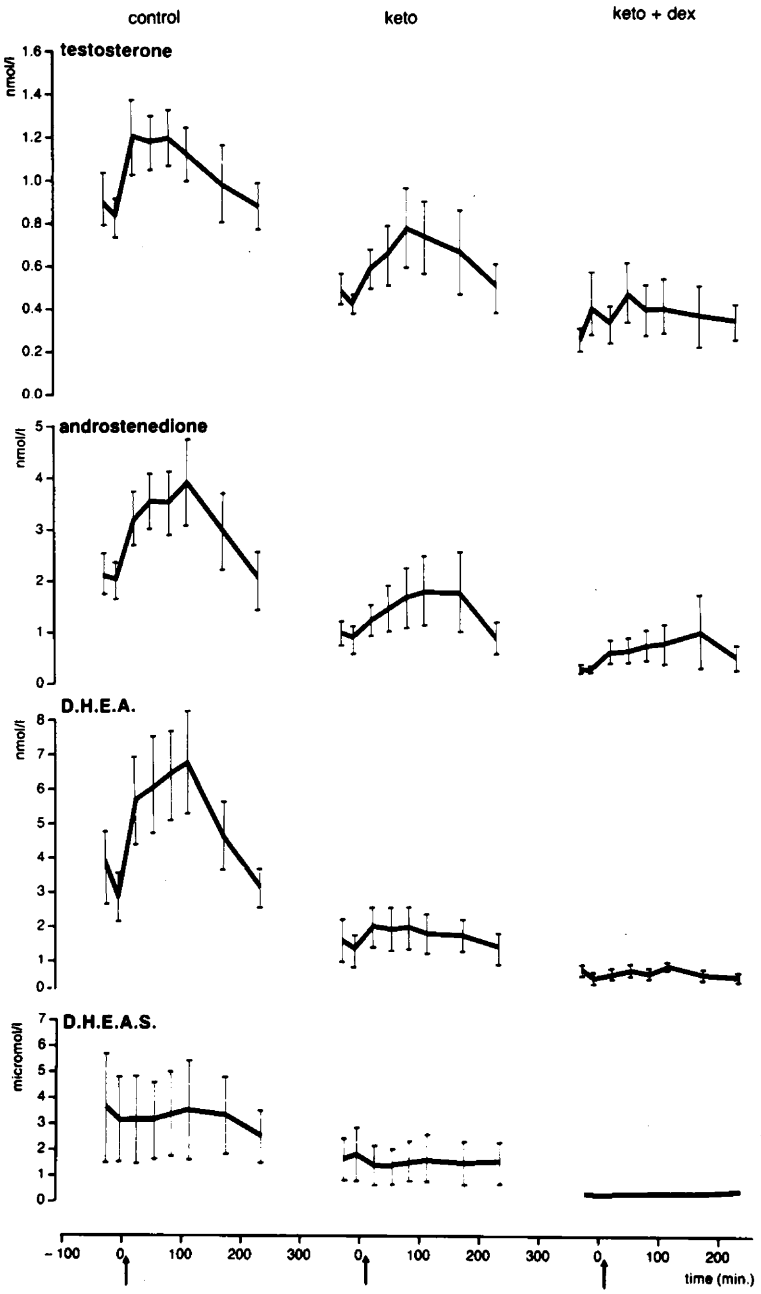

Fig. 1.

Effects of one hour of infusion of synthetic ACTH on plasma androgen levels before (control) and after high-dose ketoconazole (keto) and combined high-dose ketoconazole-dexamethasone (keto + dex) treatments in 7 previously orchiectomized patients with metastatic prostate cancer. The first two samples of each challenge were obtained before the onset of infusion (↑) and represent the basal hormonal levels. The results are expressed as mean ± SEM.

challenge was almost completely blunted by the high-dose ketoconazole treatment ($P = 0.01$) and further reduced by dexamethasone administration ($P = 0.05$), whereas plasma aldosterone was not influenced (Figs. 2 and 3). In contrast, both basal and stimulated 11-deoxycortisol ($P = 0.01$), DOC ($P = 0.01$) and, to a lesser extent, corticosterone ($P = 0.03$, basal) rose more markedly after

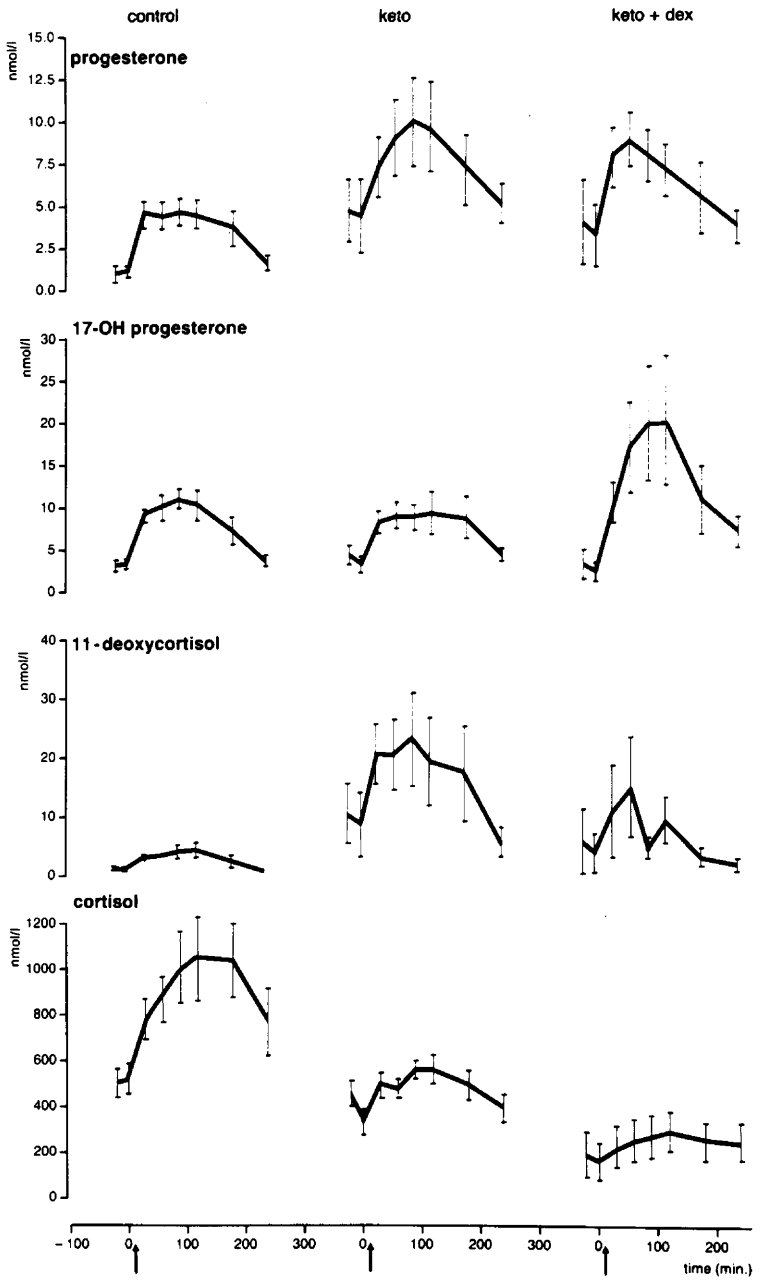

Fig. 2.

Effects of one hour of infusion of synthetic ACTH on plasma steroid levels of the glucocorticoid pathway before and after high-dose ketoconazole and combined high-dose ketoconazole-dexamethasone treatments in 7 previously orchiectomized patients with metastatic prostate cancer. The results are expressed as mean ± SEM.

ketoconazole than after placebo (Figs. 2 and 3). After combined therapy, these steroids were lowered in the same way as cortisol but showed a somewhat greater spread, particularly after adrenal stimulation (Figs. 2 and 3). Plasma 17α-hydroxyprogesterone levels were not modified by high-dose ketoconazole administration, but progesterone levels increased significantly ($P = 0.03$)

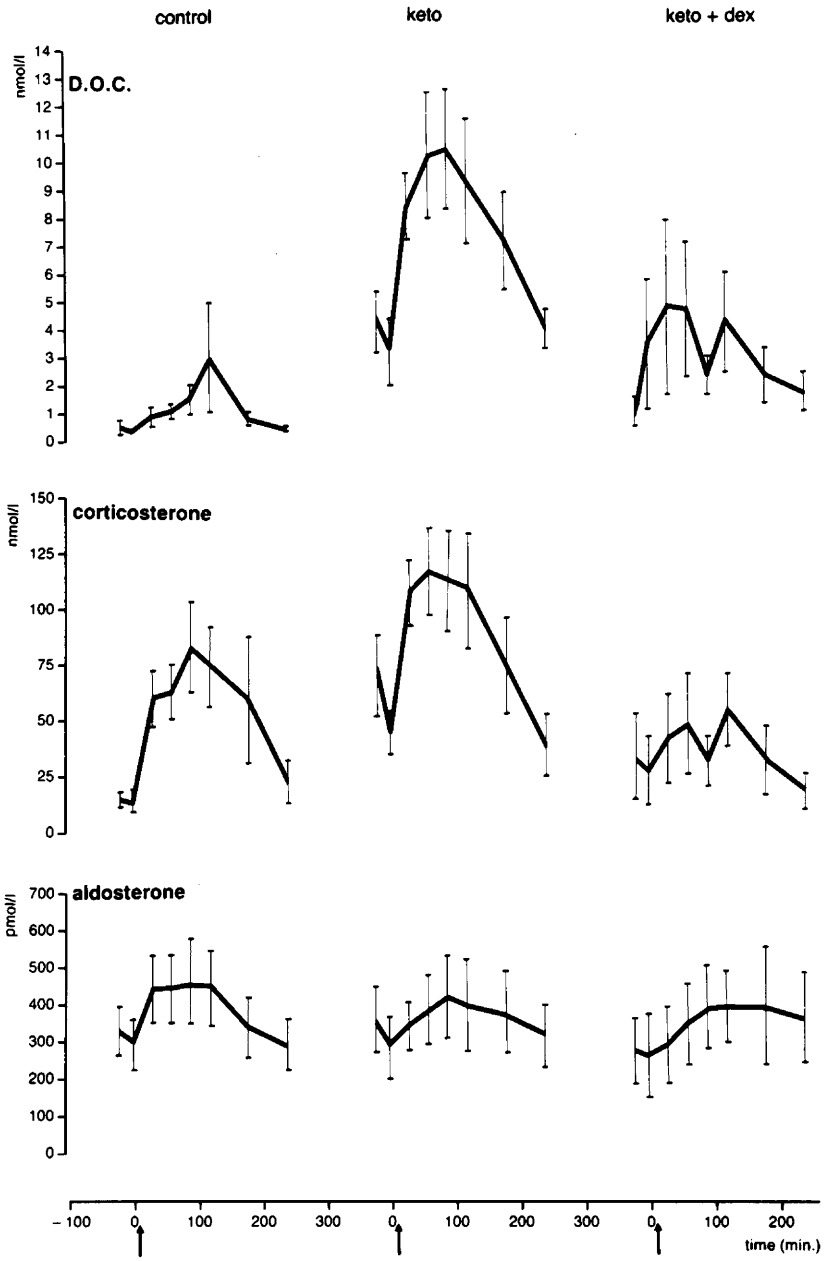

Fig. 3.
Effects of one hour of infusion of synthetic ACTH on plasma steroid levels of the mineralocorticoid pathway before and after high-dose ketoconazole and combined high-dose ketoconazole-dexamethasone treatment in 7 previously orchiectomized patients with metastatic prostate cancer. The results are expressed as mean ± SEM.

(Fig. 2). The addition of dexamethasone increased the 17α-hydroxyprogesterone response to ACTH but did not modify its basal plasma concentrations (Fig. 2). The profile of the progesterone levels was very similar to that observed with high-dose ketoconazole alone, but not significantly different from that observed in the control challenge.

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