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LONGTERM EFFECTS OF KETOCONAZOLE ON ADRENAL AND TESTICULAR ENDOCRINE FUNCTION

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We have studied the basal and synacthen (ACTH) stimulated hormone responses in 11 patients treated with ketoconazole (1200mg/day) for up to 21-33 weeks. Three patients dropped out because of side effects, and one because the drug was ineffective. Basal hormone results [± SD] are given prior to therapy (11 pts), at 2 weeks (11 pts), and at 21-33 weeks (7 pts). Testosterone (T), 13.4 ± 5.0, 4.8 ± 6.5, 3.9 ± 2.0 nmol/l, Androstenedione 4.7 ± 1.7, 1.9 ± 1.1, 1.6 ± 0.7 nmol/l, E_2 127 ± 25, 246 ± 93, 227 ± 113 pmol, SHBG 44 ± 17, 70 ± 26, 84 ± 39 nmol/l, LH 6.9 ± 2.8, 17.9 ± 8.2, 29.7 ± 15.4 u/l, Prog: <1, 6.4 ± 3.7, 4.8 ± 2.0, 17-α-OH-Prog, 3.0 ± 1.1, 6.5 ± 2.9, 7.8 ± 2.9 nmol/l. Synacthen stimulated studies show an accumulation of Prog. and 17-α-OH-Prog. Basal cortisol concentrations were normal, but maximal stimulated levels (nmol/l) were 456 ± 180 (prior), 233 ± 207 (2 wks) 305 ± 143 (21-33 wks). In two patients T levels always exceeded 5 nmol/l, and this was apparent at 2 weeks onwards. Major side effects were lethargy, and nausea, in one case relieved by corticosteroids. Ketoconazole is an effective drug in lowering T in most patients, but partial adrenocortical insufficiency is a major side effect unmasked only by stimulation studies with synacthen.

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EFFECTS OF KETOCONAZOLE TREATMENT ON HORMONE SECRETION IN METASTATIC ADRENAL CARCINOMA

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Ketoconazole is an antifungal agent, which has recently been shown to inhibit adrenal steroid synthesis. We report here the dramatic endocrine effects of ketoconazole in a patient with functioning metastatic adrenal carcinoma.

The patient was an 82-year-old woman with cushingoid features, facial hirsutism and high blood pressure. Clinical and laboratory findings were consistent with the existence of adrenal carcinoma and the diagnosis was confirmed by abdominal ultrasonography and CT scan, that demonstrated the involvement of regional lymphnodes and the presence of hepatic metastases. Since mitotane, which is considered the palliative treatment of choice in these patients, was not available in this country, we began ketoconazole treatment at the oral dose of 600 mg daily; after 4 days the dose was increased to 1 g.

Ketoconazole suppressed tumour steroidogenesis dramatically. Serum cortisol decreased within a few days from 38.6 to 20.7 µg/dl (normal values 7-19), serum testosterone from 22.3 to 1.35 ng/ml (0.15-1.1), serum androstenedione from 68.9 to 4.7 ng/ml (0.5-3.0), serum dehydroepiandrosterone sulfate from 20.0 to 1.3 µg/ml (0.1-1.9). No change was observed in hepatic and renal functions and no side effect was noticed, except nausea.

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PHARMACOLOGICAL EVALUATION OF 1-METHYL-ANDROSTA-1,4-DIEN-3,17-DIONE A NEW SELECTIVE AROMATASE INHIBITOR

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Inhibitors of estrogen biosynthesis may offer a promising method for therapeutic control of estrogen-dependent tumors in man. 1-methyl-androsta-1,4-dien-3,17-dione (SH 489) is evaluated in several in vitro studies and in many endocrine pharmacological short-term tests in mice, rats, rabbits and cynomolgus monkeys. Long-term experiments in male dogs and cynomolgus monkeys are also included to study the effect of our aromatase inhibitor on the androstenedione-induced estrogenic hyperplasia of the prostate gland. SH 489 is a competitive and a suicide inhibitor of aromatase. It does not bind to estrogen, androgen, progesterone or glucocorticoid receptors and has in mice, rats and/or rabbits no intrinsic estrogenic, antiestrogenic, androgenic, antiandrogenic, progestagenic or antigonadotropic activity. SH 489 disturbs the rat oestrous cycle, inactivates ovarian aromatase causing a decrease in the PMSG-related high serum estrogen level in rats and inhibits different androstendione-induced estrogenic effects in target tissues of female rats and in the prostate gland of dogs and cynomolgus monkeys. It is also effective in reducing serum estradiol level in male cynomolgus monkeys and young healthy male volunteers. These studies establish that SH 489 is an effective and selective aromatase inhibitor. Controlled clinical trials will now be carried out to confirm the effectiveness of this compound in the management of mammary and endometrial cancer in women and of benign prostatic hyperplasia in men.

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IN VITRO AND IN VIVO EVALUATION OF THE NEW IRREVERSIBLE AROMATASE INHIBITOR, FCE 24210

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FCE 24210 (4-aminoandrosta-4,6-diene-3,17-dione) is a new, potent irreversible aromatase inhibitor. Its properties were compared to 4-hydroxyandrost-4-ene-3,17-dione (4-OHA) in vitro and in vivo. Aromatase inhibition was evaluated by measuring ^3H_2O formed during incubation of [1β, 2β-^{3}H]androstenedione (50 nM) and the inhibitors with human placental microsomes. Irreversible aromatase inhibition was evaluated by preincubating the inhibitors and cofactors for various times with the enzyme preparation. In vivo inactivation of aromatase was studied in PMSG pretreated rats (100 I.U./rat s.c. on days -7 and -3). Twenty four hours after s.c. or p.o. administration of the inhibitors, the residual ovarian aromatase activity was measured in vitro by the ^3H_2O assay.
The in vitro IC_{50} was 120 nM for FCE 24210; 4-OHA was 4 times more potent. In preincubation studies both compounds induced NADPH-dependent enzyme inactivation, the enzyme half-lives being 4 min for FCE 24210 and 2 min for 4-OHA. In vivo studies showed that FCE 24210 inactivated aromatase by both subcutaneous and oral routes (ED_{50} 2.7 and 14 mg/kg respectively), while 4-OHA was effective only after s.c. administration (ED_{50} 3 mg/kg), aromatase being marginally inhibited at 100 mg/kg p.o. The compound showed no affinity for estrogen (rat uterus) and androgen (rat prostate) receptors.
Its in vivo properties make FCE 24210 a major advance over 4-OHA.