Effects of ketoconazole in hirsute women

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Abstract. To determine the efficacy of ketoconazole in the treatment of hirsutism, clinical and hormonal effects of this agent were evaluated in a randomized, placebo-controlled, double-blind cross-over study design. Nine hirsute women were given ketoconazole (600 mg/day) or placebo for 6 months and then crossed over. The severity of hirsutism was assessed according to the scale of Ferriman & Gallwey. Baseline serum testosterone, dehydroepiandrosterone sulphate, progesterone, estradiol, basal and stimulated cortisol and 17-alpha hydroxyprogesterone were measured. Blood was also drawn for FSH and LH levels at 0, 30, 60, and 90 min of a GnRH stimulation test. The same parameters were determined following administration of placebo or ketoconazole for 6 months. The pretreatment (28.3±0.9) and post-placebo (27.7±1.4) Ferriman-Gallwey scores were significantly higher than the post-ketoconazole score (16.6±1.3, p≤0.01). Basal and stimulated cortisol levels were not blunted after ketoconazole, but basal and stimulated 17-alpha hydroxyprogesterone levels were significantly higher, indicating sufficient enzymatic inhibition. Serum dehydroepiandrosterone sulphate and testosterone levels were significantly lowered following ketoconazole (p≤0.05). Although E2 levels did not change significantly at any time, E2: testosterone ratios were significantly higher after ketoconazole (p≤0.01), and the LH: FSH area ratio was also significantly greater than 3 after ketoconazole. It is concluded that ketoconazole significantly alleviates hirsutism by inhibiting steroid synthesis.

Ketoconazole is an imidazole derivative that can curtail gonadal and adrenal steroid biosynthesis, especially by inhibiting cholesterol side-chain cleavage and 17α-hydroxylase, 11β-hydroxylase, 18-hydroxylase, and 17,20 lyase enzymes (1). This inhibition of cytochrome P-450 enzyme systems provides the rationale for its therapeutic use in prostrate cancer (2,3), precocious puberty (4), and Cushing’s syndrome (5,6).

Because of its selective inhibition of androgen production at low doses (7), ketoconazole has also been used in the management of a few patients with hirsutism (8,9), and in non-placebo controlled studies in hirsute women (10,11).

The purpose of this study was to evaluate the effects and side effects of ketoconazole in hirsutism with a randomized, placebo-controlled, double-blind cross-over study design.

Patients and Methods

In accordance with the Helsinki II Declaration, 11 consecutive hirsute women living in Ankara gave informed consent to take part in the study after the study protocol was explained to them. None had received any treatment prior to the study. Of these patients one moved out of town one month after the study started and was lost to follow-up. Another decided to have a child three months later and was excluded from the study.

The remaining 9 women had a mean age of 24 years (range 19-41). None of them were obese. Four had regular cycles and 5 had irregular menses, with cycle lengths ranging from 30 to 180 days. One patient had given birth to 3 children, the others had not desired to give birth to children. Pelvic ultrasonography, testosterone (T) and dehydroepiandrosterone sulphate (DHEA-S) levels, and LH to FSH ratios suggested an ovarian origin of androgen production in 5 and an adrenal origin in 4 of the women. The severity of hirsutism before and during the study was assessed according to the scale of Ferriman & Gallwey (12). During the study all used nonhormonal contraception.
Study protocol
Serum samples for the analyses of DHEA-S, T, estradiol (E2) and progesterone were drawn at 09.00 h during the follicular phase in women with regular cycles and 5-10 days after the last menses in the others. A GnRH stimulation test and an ACTH stimulation test were performed on two consecutive mornings. Samples for serum cortisol and 17-hydroxyprogesterone (17-OHP) were drawn before and 4 h after the injection of 1 mg Synacthen depot® (Ciba-Geigy) for the ACTH stimulation test. Samples for LH and FSH were drawn before and 30, 60, 90 min after the iv injection of 100 µg GnRH (gonadorelin, Ferring GmbH, FRG) during the GnRH stimulation test. Areas under curves were calculated by the equation: area = t (a/2+b+c+d/2), where t is the constant sampling interval and a through d are the hormone values at each sampling time (13).

After baseline testing, ketoconazole (600 mg/day; Fungoral®, Ilitas A.S., Istanbul, Turkey) or placebo was dispensed randomly by the hospital pharmacy. Compliance to treatment was assessed by pill counts every month. After a 6-month treatment period, patients on placebo were switched over to ketoconazole and vice versa, for another 6 months. Tests were again repeated at the end of this period.

Serum total and conjugated bilirubin concentrations, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase activities, and serum cholesterol and triglyceride levels were measured biweekly for the first 2 months and then monthly during each 6-month treatment period.

Hormone assays
All hormonal analyses were done in duplicate, and all samples from an individual patient were analysed in the same assay. Serum cortisol, progesterone, LH and FSH concentrations were measured using RIA kits obtained from Amersham International (UK). Serum testosterone, 17-OHP, DHEA-S and E2 levels were determined using RIA kits obtained from ICN Biomedicals, Inc (Carson, CA). The intra- and inter-assay coefficients of variation were less than 10% for cortisol, progesterone, DHEA-S, FSH, and LH assays, and less than 12% for testosterone, E2 and 17-OHP assays.

Serum concentrations of total and conjugated bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, cholesterol, and triglyceride were measured with an autoanalyser.

Statistics
All results are reported as means ± SEM. Differences between pretreatment, post-placebo and post-ketoconazole treatment periods were calculated with a Wilcoxon signed rank test. A p-value ≤0.05 was considered significant.

Results
The baseline Ferriman & Gallwey score (28.33±0.96) did not change significantly following placebo (27.67±1.36), whereas ketoconazole treatment lowered the hirsutism score significantly (16.44±1.25; p≤0.01). The sequence of ketoconazole-placebo administration did not affect the results.

Basal cortisol levels showed a sufficient increase after Synacthen and were above 900 nmol/l (14) before treatment, after the administration of placebo, and after ketoconazole (Table 1). Although progesterone levels were higher following ketoconazole treatment (12.4±2.1 nmol/l), this did not reach statistical significance. On the other hand, both basal and post-ACTH 17-OHP levels were significantly higher after ketoconazole compared with the pretreatment and post-placebo periods (p≤0.05), indicating inhibition at the 17,20-desmolase step in the steroidogenic pathway with the dose of ketoconazole used.

Serum DHEA-S concentrations after 6 months of ketoconazole treatment (11.47±0.92 nmol/l) had decreased significantly compared with the pre-

### Table 1.
Baseline, post-ketoconazole and post-placebo hormone values.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Baseline</th>
<th>Post-ketoconazole</th>
<th>Post-placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (nmol/l)</td>
<td>483.4±58.5</td>
<td>603±58.8</td>
<td>627.7±76.1</td>
</tr>
<tr>
<td>17-OHP (nmol/l)</td>
<td>3.69±0.42</td>
<td>7.68±0.64*</td>
<td>4.02±0.61</td>
</tr>
<tr>
<td>Progesterone (nmol/l)</td>
<td>6.8±1.5</td>
<td>12.4±2.1</td>
<td>9.5±1.9</td>
</tr>
<tr>
<td>DHEA-S (nmol/l)</td>
<td>17.83±2.04</td>
<td>11.47±0.92*</td>
<td>18.22±1.54</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>3.8±0.3</td>
<td>2.0±0.4*</td>
<td>3.9±0.5</td>
</tr>
<tr>
<td>E2 (pmol/l)</td>
<td>348.78±55.2</td>
<td>377.64±31.6</td>
<td>297.79±40.1</td>
</tr>
<tr>
<td>LH area (IU·min⁻¹)</td>
<td>5941±1385</td>
<td>5327.5±840.38</td>
<td>4903.67±965.4</td>
</tr>
<tr>
<td>FSH area (IU·min⁻¹)</td>
<td>815.5±113</td>
<td>788.7±56.6</td>
<td>1019.8±150.96</td>
</tr>
</tbody>
</table>

* Denotes statistical significance (p<0.05).
treatment and post-placebo periods (p≤0.05). Testosterone levels showed a similar decline after ketoconazole (p≤0.05), whereas estradiol levels did not change following ketoconazole or placebo administration. Consequently, the estradiol:testosterone ratio was significantly high after ketoconazole treatment (p≤0.01) compared with pretreatment and post-placebo ratios. Basal serum LH and FSH levels after ketoconazole did not differ from pretreatment and post-placebo values, but the ratio of calculated LH area to FSH area of more than 3 was highly significant after ketoconazole (t=4.975, p≤0.01), but not before treatment or after placebo.

Adverse effects
In one woman serum aminotransferase levels slightly exceeded the normal upper range, but became normal 15 days later despite continued treatment. Hair loss and cheilosis were seen in 3 patients, and pruritus was noted by one. During ketoconazole treatment 7 women had frequent bleeding, ranging between 10 and 22 days, and 3 of these patients described oligomenorrhea prior to treatment and during placebo administration. One of the other 2 women with regular cycles on ketoconazole had oligomenorrhea while not on this drug.

No differences were noted in the clinical or hormonal responses of the patients receiving ketoconazole, irrespective of the source of androgen overproduction.

Discussion
The results of this study show that, in addition to its other therapeutic uses (2-6), ketoconazole at a dose of 600 mg/day, significantly alleviates hirsutism after 6 months of treatment. This is in keeping with the results of other studies that have used ketoconazole at variable doses and mostly for shorter periods of time in a limited number of patients (10,11).

Although some studies have reported either a blunted cortisol response to ACTH (15) or adrenal insufficiency (16,17), basal cortisol levels were found to be normal in other studies using ketoconazole (18). This study also did not document a blunted cortisol response to ACTH or signs of adrenocortical insufficiency during prolonged ketoconazole administration.

In accordance with the results of Martikainen et al. (10), ketoconazole blocked the 17,20-desmolase step, leading to significantly higher basal and stimulated 17-OHP levels. Similarly, serum progesterone concentrations were slightly but insignificantly increased at comparable doses.

The clinical improvement in hirsutism was accompanied by significantly lower T and DHEA-S concentrations. Although decreased T synthesis is a universal finding during ketoconazole treatment (1), unchanged DHEA-S levels during treatment of hirsutism have been reported (10). This discrepancy may be due to the difference of length of treatment (in the previous study only 4 of the women were treated for 6 months) between the two studies.

Although estradiol levels did not change after ketoconazole administration in this and other studies (2,10), E2:T ratios increase in men (19). There are no comparable reports in women. Keeping in mind the negative feedback effect of T on LH secretion (20), either significantly decreased T levels or an increased E2:T ratio may have led to the LH:FSH area ratio that was significantly greater than 3 during ketoconazole treatment. The interrelationship between these hormones and the slightly increased progesterone levels may cause the frequent bleeding that was observed during this study and necessitates cyclic estrogen administration or combination estrogen-progesterin therapy (20).

Although transient hypertriglyceridemia and, in rare cases, a reduction in serum cholesterol levels have been reported with ketoconazole (21,22), we did not observe changes in these lipids (data not shown). This may be partly due to differences in dosage.

In summary, ketoconazole effectively inhibits androgen synthesis in hirsute women and leads to clinical improvement. However, because it affects hormonal cyclicity, co-administration with estrogen to avoid frequent uterine bleeding may be recommended.

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References

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