Treatment of hirsutism with cyproterone acetate and ethinyl oestradiol*

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Twenty-one hirsute patients were treated for 6 months with 50 mg cyproterone acetate (CPA) given on days 5-15 of the menstrual cycle together with a combination oral cotraceptive containing 2 mg CPA and 35 ug *ethynil oestradiol (EEi) given on days 5-25 of the cycle. Clinical examinaton and hormone analysis were undertaken every third month. The rate of success was 80.9% for hirsutism, 93.8% for acne and 94.7% for seborrhoea. The levels of follicle-stimulating hormone, luteinizing hormone, total testosterone, estradiol and progesterone fell significantly during the treatment. In contrast there was no significant change in plasma prlactine, Cortisol and dehydroepiandrosterone sulphate levels. Side effects were rare. From the results it is concluded that CPA and EEz at dosages employed, is effective both clinically and biochemically for the treatment of hirsutism, acne and seborrhoea. [Turk J Med Res 1992,10(2): 105-109]*

KeyWords: Hirsutism, Cyproterone acetate, Ethinyl oestrodiol, Endocrine changes

Cyproterone acetate (CPA) was first used clinically by Hammerstein and Cupceancu (1). It is a synthetic sex steroid with antiandrogenic, antigonadotropic and progestagenic properties (2). To maintain control of vaginal bleeding and contraception CPA is administered with ethynil oestradiol (EE2) in a reverse sequential regimen originally devised by Hammerstein et al. (3).

CPA and EE2 has been used successfully for many years in the treatment of hirsutism, acne and seborrhoea (4,8,12).

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Because the incidence of progestational side-effects such as breast tenderness and weight gain is lower on the smaller dose, recent approach is to start treatment with 50 mg CPA (4,5,9). On the other hand, the dosage of EE2 in the majority of these studies was 50 jig daily (6,8,10). In addition, some authors claim that androgen levels remain unchanged (5,7,11,13) while others report a decrease (8,14,17) during this treatment.

The aim of this study, was to evaluate endocrine and clinical effects of CPA (50 mg and EE2 (35 ug) in female hirsutism.

MATERIALS AND METHODS

Twenty-one hirsutic women, aged 17 to 39 (mean 25.2± 1.3) years were selected for this study. None had Cushing's syndrome, ovarian-adrenal tumors, postpubertal adrenal hyperplasia or other major endocrine disorders, and none was taking any medication known to cause hirsutism, acne or hyperandrogenic states. 17 had idiopathic hirsutism and 4 had polycystic ovary syndrome (PCOS). 16

had regular menstrual periods, 5 were oligomenorrheic. Of the 21 patients with hirsutism, 16 had acne and 19 suffered from seborrhoea.

The diagnosis of PCOS was based on elevated serum LH/FSH ratio or on a increased concentrations of serum testosterone, and on ultrasonographic evaluation of the ovaries.

Before treatment each patient was assessed for hair score as described by Ferriman and Gallwey score and had a Ferriman-Gallwey score (FSG) of> 8 (18). The hair score was assessed on all occasions by the same observer.

Prior to therapy the frequency of using adjunctive therapy (electrolysis, shaving, bleaching and waxing) was recorded as the time interval.

Patients were treated for 6 months with 50 mg CPA given on days 5-15 of the menstrual cycle together with a combination oral contraceptive containing 2 mg CPA and 35 fig EE2 given on days 5-25 of the cycle, according to the principle of the reversed cycle proposed by Hammerstein and Cupceancu (3,19).

Patients were advised to avoid pregnancy, married women were fitted with intrauterine contraceptive devices. We recommended adjunctive therapy two months after initiating the treatment.

Concentrations of serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactine (PRL), oestradiol (E2), total testosterone (TT), dehydroepiandrosterone sulphate (DHEA-S), Cortisol, progesterone (P) were measured by routine radioimmunoassay (RIA) method before and at 3 and 6 months of treatmnt. Blood samples for RIA were centrifuged, and the serum stored at -20 C until analyzed. Subjects with regular menstrual periods, blood samples were taken between 8 and 10 a.m. in the follicular phase. In cases of menstrual irregularities, sampling was arbitrary.

FSH, LH and PRL were measured by double antibody RIAs using kits supplied by Amersham firm (London). Cortisol, DHEA-S, E2 and P were measured by coated tup RIAs using kits supplied by Diagnostic Products Corp (Los Angles).

Clinical observation and hormonal studies were repeated at 3 and 6 months of therapy. Patients kept a diary of menstrual pattern and frequency of hair removal.

The following parameters have been used for the clinical response to CPA and EE2: 1-A least a doubling of the longer time interval between adjuntive therapies (20). 2-A decrease of 3 or more points in the FGS (21). 3-A decreased rate of growth or ligh tening of the pigmentation of the hair (22).

Results for the group are expressed as mean ± SEM Paired t-tests were used to compare levels prior to and after treatment. Wilcoxon rank sum test was used to compare Ferriman and Gallwey hair scores.

RESULTS

CPA and EE2 was effective in 52.4% of patients with hirsutism, in 87.5% of those wiith acne and in 94.7% of those with seborrhoea at 3 months of treatment. Clinical response rates in hirsutism, acne and seborrhoea were increased at 6 months of therapy. The effect was detectable as soon as three months after the start of the treatment and it persisted until the end of trial. After 6 months of treatment, 17 of 21 (80.9%) patients with hirsutism were well satisfied with response of their hirsutism. The effects was marked on the face than on the abdomen, chest and limbs. 15 of 16 (93.8%) patients with acne were also well pleased by the end of 6 months. 18 of 19 (94.7) patients with seborrhoea noticed a considerable improvement at 6 months.

Tablo 1 shows the effect of the treatment on Ferriman and Gallwey scores. Ferriman and Gallwey scores showed a statistically singificant fell after both 3 and 6 months of treatment ($p<0.01$ and $p<0.001$, respectively). No patients had a higher

Table 1. The effect of cyproterone acetate and ethinyl oestradiol treatment on FSG*

	Before treatment	After 3 months of treatment	After 6 months of treatment
FSG	17.9± 0.7	15.2± 0.9+	11.2± 0.9+

All values are given as the mean± SEM
* FSG : Ferriman and Gallwey scores.
+ $p<0.01$ Compared with pretreatment scoring.
+ $p<0.001$ Compared with pretreatment scoring.

score after treatment. Nevertheless 4 of 21 patients were totally resistant to the therapy showing no improvemert within 6 months.

As it can be seen from Table 2, levels of FSH, LH, TT, E2 and P fell significantly both at 3 and 6 months of therapy. In contrast, there was no significant change in plasa PRL, Cortisol and DHEA-S levels.

During the treatment in ^ >f 5 patients with oligomenorrhoea developed regular menstrual periods. At 6 months of therapy 20 of 21 patients had regular menstruation. In one patient oligomenorrhoe was not improved.

During the first three months of treatment 11 patients complained of side effects. These were tiredness in 2 cases, headache in 5, nausea in 1, breast tenderness in 1, lengthened menstrual cycles in 1 and weight gain in 1. A11 of these symptoms were transient in nature and disappeared without any intervention. The patient who had weight gain responded to diet.

DISCUSSION

In the present study, 80% of patients with hirsutism had a good response to CPA+EE2 therapy. This response rate is in agreemint with previous reports (7,10,19,23) and confirm the efficacy of this treatment in the management of hirsutism. Although the dorsage of EE2 in the majority of previous studies was 50 mg daily, the present study also showed that the beneficial effect of CPA would persist when the oestrogen content was lowered to 35 mg daily.

The rate of success was 93.8% for acne and 94.7% for seborrhoea. These results are comparable to those already reported (2,3,10,17). Some anthers have reported a decrease of testosterone during CPA and EE2 treatment (8,14,17), others have not observed this effect (5,11,13). In this study, serum total testosterone levels fell singificantly. The observation by some authers of an unchanged testosterone level has been attributed to the increase of the sex hormone binding globulin (SHBG) level caused by the presence of the high dosage of oestrogens in the treatment schedule (8,11,13).

On the other hand, CPA and EE2 treatment resulted insignificantly decreased serum lelvels of FSH, LH, EE2 and P, whereas PRL, Cortisol and DHEA-S were not affected.

In addition to profound suppresive effect of estrogens, CPA, being a gestagen will inhibit gonadotropin secretion (2,7). Thus we found a significant reduction in srum LH and FSH concentratins. Previous reports have mentioned similar results (5,7,14,16).

The unchanged levels of Cortisol and DHEA-S during treatment suggest that CPA dose not affect adrenal steroid biosynthesis in the dosage used. There have been reports of an inhibitory effect of CPA on adrenocortical function in children during treatment for precocious puberty and in animal studies (24,25). Chapman et al and Holdaway et al. investigated the effect of CPA and EE2 treatment on adrenal function in hirsute women (26,27). They did not find any evidence of adrenal suppressive effect of CPA and EE2 treatment in standart dosage. On the other hand, Rubbens hasse reported some reduction in DHEA-S levels (8).

Table 2. Plasma hormone levels in hirsute women before and after treatment with CPA and EE2

Hormone	Before treatment	After 3 months of treatment	After 6 inontlis of treatment
FSH (mlU/ml)	10.9± 0.9	8.1± 0.9*	7.7± 0.9*
LH (mlU/nil)	14.5± 2.1	8.2± 1.2*	6.7± 1.3*
PRL (ng/ml)	13.6± 1.2	13.8± *13**	14.1± 1.7*
TT (ng/ml)	0.97± 0.10	0.71± 0.08*	0.70± 0.07*
Cortisol (Ug/dl)	16.0± 1.1	15.1± 1.5*	15.3± 11*
F.2 (pg/ml)	69.1± 8.1	47.6± 5.9*	43.9± 0.07*
P (ng/ml)	0.85± 0.11	,0.501 0.10*	0.48± 0.07*
DHEA-S (mg/dl)	232.5* 25.6	226.5± 26.5+	230.6+ 22.2+

The values in the table represent mean ± SEM before and after 3 and 6 monllis of treatment.

*** Significantly different from corrosponding values before treatment (P<0.01).**

+ Not significant compared with pretreatment values.

In the present study, regular cycles were found to be more common, 4 of 5 oligomenorrhoic patients developed regular menstruations. CPA and EE2 tretament provided good cycle control without beakthrough bleeding.

Various side effects, such as tiredness, headache, nausea, breast tenderness and weight gain occured in rare patients. The higher incidence of side effects has been observed in previous studies (16,17,19). Side effects produced by the high and low form of CPA therapy were compred by Belisle and Love (5). The incidence of progestational effects, such as breast tenderness, amenorrhoea and weight gain were greater in women. In the present study, both a low dose (50 mg) CPA and a reduction in the oestrogenic component of the treatment might help to reduce some of these side effects.

From the results it is concluded that CPA and EE2, at dosages employed, is effective both clinically and biochemically for the treatment of hirsutism, acne and seborrhoea.

Hirsutizmin siproteron asetat ve etinil östradiol ile tedavisi

21 hisütizmli olgu 6 ay süreyle menstrüel siklusun 5-15. günleri arasında 50 mg/gün siproteron asetat (CPA) ve siklusun 5-25. günleri arasında 2 mg CPA ve 35 mikrogram etinil östradiol (EE2) içeren bir oral kontraseptif ile tedavi edildi. Üç ayda bir olguların klinik muayene ve hormon analizleri yapıldı. Hirsutizmde %80.9, aknede %93.8 ve seborede %94.7 oranında klinik cevap alındı. Tedavi süresince plazma follikül stimüle edici hormon, lutenize edici hormon, total testosteron, östradiol ve progesteron düzeylerinde anlamlı azalmalar oluştu. Buna karşılık plazma prolaktin, kortizol ve dihedroepiandrosteron sülfat düzeylerinde anlamlı bir değişiklik olmadı. Yan etkiler nadirdi. Bu bulgularla; kullanılan dozlarda, CPA ve EEı tedavisinin hirsutizm, akne ve sebore üzerine etkili olduğu sonucuna varıld.

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Anahtar Kelimeler: **Hirsutizm, Siproterone asetat, Etinil östradiol, Endokrin değişiklikler**

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