THE EFFECT OF CYPROTERONE ACETATE ON THE PITUITARY-ADRENAL AXIS IN HIRSUTE WOMEN

By

ABSTRACT
The functioning of the hypothalamo-pituitary-adrenal axis was assessed in 10 adult women with idiopathic hirsutism treated for 2 weeks with the anti-androgen cyproterone acetate in a dose of 50 mg b. d. daily and in 4 patients treated for at least 3 months. Basal plasma ACTH and cortisol levels and the cortisol response to 8 h ACTH infusion were comparable before and during short-term treatment. The plasma ACTH and cortisol responses to insulin induced hypoglycaemia before and during anti-androgen therapy also were of the same order of magnitude. In the 4 patients treated for at least 3 months also no suppressive effect of the anti-androgen on basal plasma cortisol levels was observed. From these data the conclusion seems warranted that short-term cyproterone acetate treatment in the given dose not significantly influences pituitary-adrenal function in adult women with idiopathic hirsutism.

The synthetic progestational steroid 1\(\alpha\),2\(\alpha\)-methylene-6-chlor-4,6-pregnadien-17\(\alpha\)-ol-3,20-dion-17\(\alpha\)-acetate (cyproterone acetate) is a potent androgen antagonist, which acts by competing with endogenous and exogenous androgens on the target organ. Except for its anti-androgenic action, in recent years an inhibitory effect of cyproterone acetate on the adrenal gland weight and function has been established in laboratory animals (guinea pigs, rats, mice, hamsters) treated for short time (from 2 h to 4 weeks) with the anti-androgen in doses
varying from 1 mg to 50 mg/kg body weight (Winkler & Harkness 1964; Domenico & Neumann 1967; Neri et al. 1967; Denef et al. 1968; Schreiber et al. 1971; Broulik & Starka 1975; Zieger et al. 1976; Purvis et al. 1976; Girard & Baumann 1975). This effect has been ascribed to a corticosteroid like action of cyproterone acetate (Broulik & Starka 1975). Very recently also evidence for adrenal insufficiency has been found in children treated with cyproterone acetate because of precocious puberty (Girard & Baumann 1975; Fried et al. 1976; Jeffcoate et al. 1976; Zurbrügg 1976; von Mühlendahl et al. 1977).

To our knowledge no systemic reports have been published on the effect of short term cyproterone acetate treatment on the pituitary-adrenal function in adults. This study reports on the pituitary ACTH and adrenal cortisol reserve of patients with idiopathic hirsutism treated with cyproterone acetate for at least 2 weeks.

MATERIALS AND METHODS

Cyproterone acetate (Androcur® Schering, 50 mg twice daily) was administered orally to 10 patients with idiopathic hirsutism (age 22.5 ± 6.6 ± years, range 18 to 40 years) during at least 2 weeks, starting treatment on the 5th day of the menstrual cycle. To assess the adrenal cortisol reserve, before and on the last day of treatment ACTH (Synachten® Ciba, 1/4 mg in 500 ml 5% glucose) was infused between 8:00 and 16:00 h and blood samples for plasma cortisol measurement were taken before and after the infusion. Before and on the penultimate day of cyproterone acetate treatment the effect of insulin induced hypoglycaemia on plasma ACTH and cortisol levels was assessed. Blood samples for glucose, cortisol and ACTH determination were taken at -15, 0, 20, 30, 45, 60 and 90 min after intravenous injection of 0.1 U insulin/kg body weight. The hypoglycaemia stimulus was considered adequate if the plasma glucose levels (measured by Autoanalyzer) fell below 40 mg/100 ml and this was achieved both before and during cyproterone acetate treatment in 7 patients. In 4 of the patients treated with cyproterone acetate (50 mg twice daily) for at least 3 months, plasma cortisol levels were measured before and after 1/2, 2 and 3 months of treatment.

Plasma ACTH levels were measured by radioimmunoassay. Wellcome's antiserum was used in a final dilution of 1:50,000. ACTH 1–24 was iodinated according to McElhinney & Schulster (1974) obtaining specific activities of about 300 μCi/mg. The standard used was human ACTH 1–39 synthesized by Ciba. Bound and free hormone were separated by charcoal-Dextran. Plasma was extracted with silicic acid (100 mesh, Mallinckrod) according to Liotta & Krieger (1975) omitting the acidification of the plasma. ACTH was eluted from the silicic acid with acidified acetone. The coefficient of variation within assay was 15% and between assays 17%.

Plasma cortisol levels were measured by radioimmunoassay. Corticosteroid binding globulin was denatured by incubation at 70°C for 1 h after dilution of the plasma with ethanol/water (1:20). Antibody (raised against cortisol-21-hemisuccinate coupled to bovine serum albumin, obtained by courtesy of Dr. Vecsei (University of Heidelberg) and tracer [3H]cortisol were added and after incubation at 4°C for 18 h bound and free hormone were separated by Dextran-coated charcoal. Replicate analysis of a plasma pool with a cortisol level of 6 μg/100 ml disclosed intra- and inter-assay
coefficients of variation of 5 and 10 %, respectively. The inter-assay duplicate variation determined from determination of samples containing 3.5 to 7, 7 to 10 and 10 to 20 μg/100 ml were 8.6, 7.4 and 4.3 %, respectively (n = 17).

Statistical analysis was performed using Wilcoxon's signed rank test (P-values denoted by P) and Wilcoxon's two sample test (P-values denoted by P*).

RESULTS

1. Basal plasma cortisol levels and the effect of ACTH infusion (Fig. 1)

The mean basal plasma cortisol levels in the 10 patients with idiopathic hirsutism before (11.2 ± 2.8 SD μg/100 ml) and during cyproterone acetate treatment (12.7 ± 4.3 μg/100 ml) did not differ significantly (P > 0.10). Plasma cortisol increments in response to ACTH infusion (35.3 ± 10.5 before and 31.6 ± 7.1 μg/100 ml during treatment) also were not significantly different (P* > 0.10) before and during therapy.

2. Effect of insulin induced hypoglycaemia on blood glucose, plasma ACTH and cortisol levels. (Fig. 2)

The hypoglycaemia responses to insulin before and during cyproterone acetate treatment were about equal with lowest blood glucose levels of 31.1 ± 7.0 and 31.2 ± 4.0 mg/100 ml, respectively (P > 0.1) 20 min after the insulin injection.

The mean basal plasma ACTH levels were 14.2 ± 8.0 before and 9.1 ± 3.1 pg/ml during cyproterone acetate therapy (P > 0.10). In response to the insulin
Fig. 2.

Effect of insulin induced hypoglycaemia on plasma ACTH and cortisol levels in 7 adult women with idiopathic hirsutism before (●——●) and during (○——○) cyproterone acetate treatment (50 mg b. d.) for 2 weeks.

induced hypoglycaemia the mean plasma ACTH levels rose to 156 ± 162 pg/ml before and to 138 ± 66 pg/ml during treatment (P > 0.10). In 4 patients the maximal ACTH increment was higher during than before treatment, in 3 patients lower.

The mean basal plasma cortisol levels at time 0, respectively, were 10.5 ± 3.6 before and 12.9 ± 3.6 μg/100 ml (P > 0.10) during treatment. After a statistically significant initial fall to 9.4 ± 2.8 and 9.8 ± 1.8 μg/100 ml at 20 min after insulin injection, plasma cortisol levels at 60 min maximally rose to 18.4 ± 5.7 μg/100 ml before and 23.1 ± 5.1 μg/100 ml during treatment (P > 0.10). The hypoglycaemia preceded the AGTH peak by 12.8 ± 5.7 min before and by 17.1 ± 7.5 min during cyproterone acetate therapy (P* > 0.10), whereas the corresponding time intervals between the ACTH and plasma cortisol peaks were 20 ± 20 min before and 25 ± 19 min during the anti-androgen treatment (P* > 0.10).
3. **Effect of 3 months antiandrogen therapy**

The mean plasma cortisol levels in the 4 patients treated with cyproterone acetate for at least 3 months were 12.3 ± 3.5 μg/100 ml before and 13.7 ± 1.8, 13.3 ± 5.1 and 13 ± 1.2 μg/100 ml (respectively after 1/2, 2 and 3 months of treatment) ($P > 0.10$).

**DISCUSSION**

Two weeks treatment with the anti-androgen cyproterone acetate in a dose of 50 mg twice daily not significantly influenced either basal plasma cortisol and ACTH levels or the pituitary ACTH and adrenal cortisol reserve of adult women with idiopathic hirsutism.

These data are in contrast with findings in male and female laboratory animals (rats, mice and hamsters) in which short term cyproterone acetate administration (7 to 28 days) in doses varying from 1 to 100 mg/kg body weight induced adrenal atrophy (Neri et al. 1967; Denef et al. 1968; Schreiber et al. 1971; Broulik & Starka 1975; Zieger et al. 1976), decreased the plasma corticoid binding capacity (Denef et al. 1968) and lowered the plasma corticosterone (Neri et al. 1967; Denef et al. 1968; Girard & Baumann 1975) and urinary 17-hydroxycorticosteroid levels (Winkler & Harkness 1964). The cyproterone acetate induced adrenal weight loss could be prevented by simultaneous ACTH administration (Neri et al. 1967), suggesting that cyproterone acetate primarily suppressed pituitary ACTH release. Direct evidence for this thesis was obtained from studies by Girard & Baumann (1975), who demonstrated a cyproterone acetate induced decrease of plasma and pituitary ACTH in albino rats.

Very recently adrenal insufficiency also has been reported in children with precocious puberty, treated with cyproterone acetate in doses varying from 60 to 210 mg/m²/day for 0.1 to 5.8 years (Girard & Baumann 1975; Fried et al. 1976; Zurbrügg 1976; Jeffcoate et al. 1976; von Mühlendahl et al. 1977). Basal plasma cortisol levels after therapy were low and showed a blunted response to ACTH stimulation (Fried et al. 1976; Jeffcoate et al. 1976). In contrast with these reports Angeli et al. (1976) treating 7 children with precocious puberty with 50 mg cyproterone acetate daily did not find evidence of adenocortical suppression even after 8 to 36 months of treatment. We have no explanation for these discrepancies, although it has to be realized, that precocious puberty in many studies is a syndrome caused by variable pathologies (Jeffcoate et al. 1976) rather than a well defined disease entity and that in the studies, dealing with adverse effects of cyproterone acetate normality of pituitary reserve of ACTH at the start of the study was not always documented very well. In the adult hirsute women from the present study, treated with 100 mg cyproterone acetate daily for 2 weeks, basal plasma cortisol and ACTH levels and the
cortisol and ACTH responses to exogenous ACTH and/or insulin induced hypoglycaemia were adequate and comparable to the pre-treatment values. In 4 of the patients sustained cyproterone acetate treatment for 3 months also not significantly influenced basal plasma cortisol levels. These data therefore do not point to a corticoid-like suppressive action of cyproterone acetate in the given dose on the pituitary-adrenal function in these adult women. One explanation for the discrepancy with the literature data might be that the suppressive effect of cyproterone acetate on pituitary-adrenal function is time- and dose-dependent (von Mühlendahl et al. 1977). The latter investigators could not demonstrate adrenocortical suppression in 2 out of 9 children with precocious puberty treated either with low doses of cyproterone acetate or for only short time. A higher sensitivity of the pituitary-adrenal axis to the suppressive effect of the anti-androgen in laboratory animals and children than in adult men also may play a role. Von Mühlendahl et al. (1977) and Jeffcoate et al. (1976) found no adrenocortical suppression or impaired pituitary ACTH reserve in 2 respectively 1 adult man treated with cyproterone acetate for 1 to 3 months. Such hypothesis contrasts however, with the data of Angeli et al. (1976) who did not find lowering of the basal plasma cortisol levels during cyproterone acetate treatment of children with precocious puberty. In view of these controversial data, further systemic studies on the effect of short- and long-term high or low dose cyproterone acetate treatment on the hypothalamo-pituitary-adrenal function in children and adults are necessary, before definite conclusions can be drawn.

REFERENCES

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