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INFLUENCE OF CORTICOTROPHIN ON URINARY 17-KETOSTEROID EXCRETION IN ADRENALECTOMIZED FEMALES

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ABSTRACT

Urinary excretion of 17-ketosteroids was measured during dexamethasone substitution followed by ACTH (Synacthen Depot®, 1 mg daily) in 10 non-virilized adrenalectomized women. No significant changes could be demonstrated indicating ovarian androgenic dependence of ACTH in non-virilized females.

The use of the suppression tests has previously been accepted in determining whether the adrenal glands and/or the ovaries are the site of excessive androgen production. Recent studies by Kirschner & Jacobs (1971) cast doubt on the use of exogenous corticoid suppression tests in evaluating the site of androgen excess in hirsutes. Apparently, diminished androgen production resulting from corticoid administration cannot be interpreted as indicating adrenal origin of excessive androgen. We thus thought it of value to investigate whether ACTH administration to adrenalectomized subjects would influence the urinary excretion of 17-ketosteroid (17-KS) and indicate the existence of ACTH-dependent androgen production from other sources than the adrenal glands.

MATERIAL AND METHODS

Ten females were investigated (Table 1). Total adrenalectomy due to pituitary ACTH-dependent Cushing's syndrome had been carried out 3 to 8 years before this investigation. Clinical remission was observed in all patients and none of the patients were...
hirsute or virilized. They were maintained on 37.5 mg cortisone acetate and 0.1 mg fluorohydrocortisone acetate daily.

In 4 patients (Nos. 1-4. Table 1) the menstrual cycle had been regular following remission. These patients were studied during the second half of the menstrual cycle. In the remaining 6 patients (Nos. 5-10) menopause had occurred at the time of examination.

Following 2 days of dexamethasone (DXM) administration in low dose (0.5 mg six-hourly) ACTH (Synacthen Depot® 1 mg) was given intramuscularly on each of 3 days during continuous DXM administration. Total F, total B and total 17-KS were measured in 24-hour urinary specimen on the 2nd day of DXM (control) and the 3rd day of ACTH.

Total F consists of tetrahydrocortisol, allo-tetrahydrocortisol, tetrahydrocortisone, Reichsteins compound U, cortisol and cortisone. Total B consists of tetrahydrocorticosterone, allo-tetrahydrocorticosterone, tetrahydro-11-dehydrocorticosterone, corticosterone and 11-dehydrocorticosterone. Total F and B were measured according to a modification of the method of Cost & Veger (1962) described by Nielsen et al. (1969) based on paper chromatographic separations of the steroids followed by quantitation on the paper after the blue-tetrazolium reaction. Normal range for total F is 1.3-10.0 mg/24 h or 1.2-6.1 mg/g creatinine. Normal range for total B is 0.12-1.00 mg/24 h or 0.12-0.74 mg/g creatinine. The sensitivity, in terms of the lowest value which can be significant distinguished from 0-value, is 0.005 mg/24 h. The coefficient of variation is 16 % of duplicate determinations (Nielsen et al. 1969).

Total 17-KS was determined according to Vestergaard (1951) and consists of dehydroepiandrosterone, androsterone, aetiocholanolone, 11-keto-aetiocholanolone and 11-hydroxy-aetiocholanolone. Normal range for total 17-KS is 4.3–15.4 mg/24 h. The sensitivity, in terms of the lowest measurable values is approximately 1 mg/24 h. The accuracy of the method is expressed by s = 0.04 mg/l urine obtained from duplicate determinations on the same day in the range 1 to 5 mg/24 h.

RESULTS

In Table 1 the results are given in both absolute terms and compared to the creatinine excretion.

The spontaneous excretion of total F was negligible in all patients. During ACTH stimulation no significant difference was observed in 9 of the patients. In one patient (No. 5) a small increment was found. Similar changes were found when compared to the creatinine excretion.

The spontaneous excretion of total B was undetectable or negligible in all patients. During ACTH stimulation no significant difference was found except in patient No. 5 who exhibited an increment corresponding to the increment in total F.

The excretion of 17-KS showed only minimal and unsystematical changes, except in patient No. 8 and 1 where a relatively pronounced decrease and increase, respectively, was found. Neither could any systematic changes in 17-KS subfractions be demonstrated.
Table 1.
Cortisol and cortisol metabolites (total F), corticosterone and corticosterone metabolites (total B) and total 17-ketosteroids (17-KS) in 24 h urine specimens during dexamethasone substitution (DXM) followed by ACTH stimulation in 10 adrenalectomized females.

<table>
<thead>
<tr>
<th>Code</th>
<th>Age in years</th>
<th>Total F</th>
<th>Total B</th>
<th>Total 17-KS</th>
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<tbody>
<tr>
<td></td>
<td>DXM</td>
<td>DXM + ACTH</td>
<td>DXM</td>
<td>DXM + ACTH</td>
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<tr>
<td>1</td>
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<td>mg/24 h</td>
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<td>0</td>
<td>0.1</td>
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<tr>
<td></td>
<td>mg/24 h</td>
<td>-0.05/0.42</td>
<td>0/0.02</td>
<td>-1.1/0.6</td>
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<td>mg/g creat.</td>
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<td>0.01</td>
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<td>mg/g creat.</td>
<td>-0.02/0.39</td>
<td>0/0.02</td>
<td>-2.4/1.3</td>
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</table>
DISCUSSION

It is well recognized that urinary neutral 17-KS arise primarily from adrenal androgens. However, in the adrenalectomized female significant plasma levels of androgens originating from the ovary have been demonstrated (Abraham & Chakmakjian 1973; Grodin et al. 1973). Likewise, urinary 17-KS are measurable in patients with Addison’s disease (Knowlton 1971).

Ovarian androgen secretion in hirsutes has been found to be dexamethasone-suppressible suggesting indirectly ACTH-dependence (Kirschner & Jacobs 1971). To our knowledge no data exists giving direct evidence for ACTH-dependent ovarian androgen secretion in normal women or hirsutes, although Knowlton (1971) found only small changes in 17-KS after ACTH stimulation in 10 patients of unmentioned sex with Addison’s disease.

In the present study total adrenalectomy was documented according to specific adrenal corticosteroid-metabolites measured before and during ACTH stimulation. This subject has been further elucidated in another paper (Blichert-Toft et al., in press). Hence, based on our observations, any noteworthy stimulatory effect of ACTH on the ovarian contribution to urinary 17-KS has not been demonstrated.

The findings of Kirschner & Jacobs (1971) of a suppressibility of plasma testosterone and androstenedione by dexamethasone in hirsute females whose major source of these androgens were the ovaries, may therefore be due to an altered adrenal and/or ovarian biochemical pathology connected with this syndrome.

In this study 6 of the females were post-menopausal. However, it is known from biosynthetic studies that androgen production is continued after the menopause and takes place in the stromal tissue (Plotz et al. 1967; Mattingly & Huang 1969). Furthermore, this androgen formation also seems to show a gonadotrophin-dependence similar to the androgen production in normal ovaries (Plate 1963). Thus, it seems permissible to include these 6 patients in the series together with the 4 normal menstruating women. In addition, the cessation of androgen production from the follicles after the menopause seems to be of minor significance as no systematic change in total 17-KS excretion between normal menstruating and post-menopausal women was found in this study (Table 1).

It is concluded that no ACTH-dependence of ovarian androgen production of any clinical significance has been established.

REFERENCES


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