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Isotretinoin, Tetracycline and Circulating Hormones in Acne

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Isotretinoin, used to treat severe acne, has been shown to induce hormonal changes, especially to reduce 5α-reductase in the production of the tissue-derived dihydrotestosterone (DHT) metabolite 3α-Adiol G. However, the effects of isotretinoin on other pituitary, adrenal or gonadal hormones have not been thoroughly elucidated. In the present study, isotretinoin administered at a dose of 0.5 mg/kg/day for 4 weeks caused no marked changes in the serum levels of pituitary, adrenal or gonadal hormones or 3α-Adiol G in patients with severe papulopustulotic acne ($n=19$). After 12 weeks of therapy, there was a decrease in the levels of the precursor androgens androstenedione, testosterone and 3α-Adiol G in 6/9 patients. Acne improved after 4.5 months in all but 2 male patients, who had very low serum hormone binding globulins (SHBG) and a high free androgen index (FAI). Isotretinoin did not affect the elevated LH/FSH ratio in a patient with the polycystic ovarian syndrome (PCOS); nor did it change the high FAI or low SHBG in the male patients. For comparison, tetracycline had no effects on the serum hormonal levels of patients with mild acne ($n=19$) after 7 days of treatment. This study confirms that the effects of isotretinoin on the serum hormone levels are small and unlikely to be of relevance for the resolution of acne or the suppression of sebum excretion. ***Key words:*** *5α-androstan-3α, 17β diol glucuronide (3α-Adiol G); dehydroepiandrosterone sulphate (DHEAS); testosterone; SHBG; pituitary hormones.*

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Although acne is an androgen-dependent disease and cannot develop without androgen action, as, for example, in congenital 5α-reductase deficiency (1), the details of the action whereby androgens induce acne are not yet completely understood. Recent studies show that acne increases early upon advancing pubertal maturation and is associated with a higher concentration of adrenal androgen DHEAS in adrenarche (2, 3). In tissues, testosterone and DHT bind to the androgen receptor, and other androgens have to be converted first to testosterone to be capable of receptor binding (4). The DHT metabolite 5α-androstan-3α, 17β-diol glucuronide (3α-Adiol G) is often elevated in patients with acne and hirsutism (5, 6), and it has been viewed as a good indicator of peripheral androgen action and 5α-reductase activity (6, 7). Furthermore, 5α-reductase activity is elevated in acne areas (8).

Some studies have revealed that treatment of acne with isotretinoin is followed by inhibition of 5α-reductase and a decrease in the production of the tissue- derived DHT metabolite 3α-Adiol G (9, 10). Tetracyclines inhibit bacterial lipolysis (11) and granuloma formation (12) and may disturb estrogen action during hormonal treatments. They have also been shown to decrease serum testosterone by 20% in male patients with acne (13). However, the effects of tetracyclines on peripherally derived DHT metabolites, such as 3α-Adiol G, have not been studied. Hormonal changes induced by drugs are usually rapid, and the alterations in binding proteins can be seen even within a couple of weeks (14, 15).

This study was planned to elucidate the effects of isotretinoin and tetracycline on circulating or peripherally derived hormone levels.

PATIENTS AND METHODS

Patients

Eight women, mean age 24.5±5.5 years (range 18–34 years), and 11 men, mean age 20.9±4.9 years (range 16–33 years), suffering from persistent severe inflammatory acne, were recruited for the study and given 0.5 mg/kg per day of isotretinoin (Roaccutane, Roche products Ltd) for 3 to 8 months, until the acne resolved.The patients had no other diagnosed diseases.The patients had had no hormonal treatment within 3 months before the study and no antibiotics for 1 month before the study. The females were not hirsuted and had no androgenetic alopecia. One patient had menstrual irregularities. The female patients did not use oral contraceptives for 3 months before and during the treatment.

Tetracycline hydrochloride (Oricyclin, Orion Pharmaceuticals) 500 mg x 2 per day was given for 7 days to 10 women aged 14–26 years (mean 21±3.7) and 9 men aged 16–38 years (mean 22.2±6.6) with mild acne.

Methods

The serum samples were collected at baseline ($n=19$), after 4 weeks ($n=19$), after 12 weeks ($n=9$) and after 16 weeks ($n=2$) of treatment with isotretinoin, generally at 8–10 o'clock in the morning, and from the females generally on cycle days 3–6 or 16–22 and stored at −20°C before analysis.

The degree of acne was estimated using the scale developed by Plewig & Kligman in 1993 (16) by counting the number of comedones and papules/pustules on each side of the face before the treatment and after 3, 4, 5, 6 or 8 months of treatment, until at least an 85% resolution of the acne was observed. The patients with severe acne had numerous comedones >50, papules/pustules >30 and >3 nodular lesions. None of the patients had severe cystic acne. In addition, patients with extensive areas of acne on the back and the chest areas were recruited to demonstrate more clearly the possible tissue-derived changes in testosterone or the association of the DHT metabolite (= 3α-Adiol G) with a wide acne area on the skin. Four female patients had only severe facial acne. The patients with mild acne had <20 comedones, <10 active papules/pustules and no nodular lesions on the face.

Hormone analyses: testosterone, cortisol (Orion Diagnostica, Espoo, Finland), androstenedione, dehydroepiandrosterone sulphate (Diagnostic Products Corporation, Los Angeles, USA) and 5α-androstan-3α, 17β-diol glucuronide (Diagnostic Systems Laboratories INC., Webster, USA) were determined by radioimmunoassays. LH, FSH and SHBG were determined by time-resolved fluoroimmunoassay (Wallac oy, Turku, Finland) and prolactin was determined by an automated chemiluminescence system (Ciba-Corning ACS-180, Medfield, USA), according to the instructions given by the manufacturers. The serum-free androgen index (FAI) was calculated using the equation : 100 × T (nmol/l) divided by SHBG (nmol/l).

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Statistics

The differences between the first, second and third measurements of hormone concentrations were tested using the paired *t*-test or the sign test when appropriate. The differences in the baseline hormone levels between the isotretinoin group and the tetracycline group were analysed by Student's *t*-test.

The differences during the treatment between the isotretinoin and tetracycline groups were compared with the two-sample *t*-test or the Mann-Whitney test when appropriate.

RESULTS

A resolution of acne greater than 85% with a dose of 0.5 mg/kg per day of isotretinoin was achieved within 4.5 months in 17/19 patients, within 6 months in one patient and within 8 months in one patient.

The pretreatment levels of testosterone in male patients ($n=11$) and androstenedione in female patients ($n=8$) were higher in the group with severe acne compared to the male patients ($n=9$) and female patients ($n=10$) with mild acne, (Student's *t*-test, $p<0,05$).

Effect of isotretinoin on serum hormone levels

The androgen precursors androstenedione and DHEAS, active androgen testosterone or the tissue metabolite 3α-Adiol G were not altered significantly by 4 weeks of isotretinoin treatment (Table I). In spite of the decline in the concentrations of testosterone, androstenedione and the tissue-derived metabolite 3α-Adiol G in 6 out of 9 patients during a 12-week treatment period, isotretinoin had no statistically significant effect on the serum levels of the pituitary hormones LH, FSH and PRL or serum cortisol, androstenedione, DHEAS and testosterone or 3α-Adiol G and the sex hormone-binding protein SHBG (paired *t*-test or sign test). The androstenedione drop in the group of female patients with severe acne was near borderline significance ($p<0,07$).

The individual hormonal status was remarkably stable in most cases. The female patient aged 19 with extensive nodular acne and irregular menstruation, but no hirsutism, had bilateral polycystic ovaries in ultrasonography. During isotretinoin treatment her acne cleared and androstenedione and testosterone normalized, but the LH/FSH ratio remained elevated (Table II).

The 2 male patients aged 19 and 21 with extensive inflammatory acne, who responded poorly to isotretinoin, had very high FAI levels–nearly twofold (150 and 200) compared to the baseline mean level of 106 in this study–and low SHBG levels (12.7 and 7.6) (the mean level being 28 nmol/l). Normal hormonal levels were also noted in cases of severe papulopustular acne.

Effect of tetracycline hydrochloride on serum hormone levels

Tetracycline hydrochloride at a dose of 1 g per day for 7 days did not cause any significant changes in the hormonal levels of 19 patients with mild acne (not shown).

DISCUSSION

Increased sebum excretion and hypercornification of pilosebaceous ducts are basic alterations in acne (17, 18). However,

Table I. *Serum hormone concentrations (mean ± SD) of 11 male patients and 8 female patients with severe acne before treatment and after 4 and 12 weeks of therapy with isotretinoin 0.5 mg/kg per day*

Age	Males 20.9 ± 4.9			Females 24 ± 5.5		
Week	Baseline	week 4	week 12	Baseline	week 4	week 12
n	*n* = 11	*n* = 11	*n* = 7	*n* = 8	*n* = 8	*n* = 2
Hormone and reference range M = males F = females						
Testosterone M 9–35 F 1–3.1 nmol/l	22.2 ± 8.4	24.1 ± 7.4	18.3 ± 4.5	2.9 ± 0.8	2.4 ± 1.4	2.1 ± 0.6
SHBG M 10–60 F 30–120 nmol/l	27.0 ± 17.0	28.6 ± 16.1	23.5 ± 19.0	61.3 ± 16.1	52.3 ± 17.1	58.4 ± 1.1
FAI M 30–180 F 1.4–7.3	106 ± 44	97 ± 40	108 ± 61	4.7 ± 2.0	4.7 ± 2.1	3.6 ± 0.9
Androstenedione M 2–10 F3–15 nmol/l	9.2 ± 4.2	9.4 ± 5.6	6.0 ± 3.3	12.0 ± 4.8	11.3 ± 6.7	6.2 ± 0.8
DHEAS M&F 1–9 µmol/l	7.5 ± 4.2	7.6 ± 4.4	6.8 ± 2.7	4.8 ± 1.9	5.2 ± 1.6	4.0 ± 0.9
Cortisol M&F 0.15–0.65 µmol/l	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.1	0.5 ± 0.2	0.4 ± 0.1	0.5 ± 0.2
LH M 2–12 U/l	3.9 ± 1.7	4.0 ± 1.2	3.5 ± 1.0	4.0 ± 1.7	7.2 ± 5.5	8.9 ± 6.2
FSH M 2–12 U/l	3.8 ± 3.5	3.7 ± 3.2	4.0 ± 3.4	2.6 ± 1.0	4.6 ± 1.4	5.2 ± 0.5
Prolactin M < 320, F < 530 mU/l	204 ± 59	223 ± 131	176 ± 80	317 ± 160	270 ± 114	119 ± 10
3α-Adiol G M 10–25 F 1.3–8 nmol/l	15.6 ± 4.2	15.4 ± 5.0	12.8 ± 3.2	9.0 ± 3.7	7.7 ± 3.2	7.2 ± 4.7

Table II. *Hormonal levels of a female patient with severe acne and PCOS and her hormonal responses to isotretinoin 0.5 mg/kg per day for 4 and 12 weeks*

A female of 19 years with PCOS

Hormone	Prolact mU/l	LH U/l	FSH u/l	SHBG nmol/l	Testos nmol/l	FAI	Andros nmol/l	DHEAS μmol/l	Cortisol μmol/l	3αAd G nmol/l
Baseline	254	4.6	4.7	76	3.8	5.0	18.5	4.2	0.64	13.0
4 weeks	340	13.0	4.9	82	5.1	6.2	23.2	4.2	0.61	10.5
12 weeks	129	13.0	4.4	58	2.5	4.3	6.7	3.3	0.43	10.5

increased sebum excretion may also occur without acne, as in Parkinsonism or acromegaly (19).

Testosterone is converted to DHT via 5α-reduction only in peripheral tissues, such as the skin and the prostate, and 3α-Adiol G is a DHT metabolite (4). Basal sebocytes contain androgen receptors (18).When Lookingbill et al. in 1988 (9) noticed a decrease in the levels of 3α-Adiol G after 12 weeks of treatment at a dose of 1 mg/kg/day of isotretinoin, they thought it likely to be due to a reduction in the amount of sebaceous tissue. Rademaker et al. in 1991 (10) found a decreased urinary 5α/5β ratio in 7 female patients after 12 weeks' treatment with 1 mg/kg/day of isotretinoin, and they concluded that isotretinoin may inhibit 5α-reductase.

Four weeks' or three months' treatment with isotretinoin did not markedly change the levels of serum pituitary, adrenal and gonadal hormones or the peripherally derived DHT metabolite 3α-Adiol G in the present study, suggesting that isotretinoin has hormone-independent action on the sebaceous glands.

Unquestionably, acne is hormone-dependent and especially in early puberty connected with higher DHEAS levels compared to healthy controls (2). Antiandrogens and estrogens are beneficial in acne, and cyproterone acetate decreases the serum levels of 3α-Adiol G (21) and also sebum excretion (22).

In our study, the decrease in androgen levels, when present, occurred in precursor androgens, testosterone and 3α-Adiol G in the same patients, in agreement with previous studies where DHEAS, androstenedione and testosterone displayed a positive correlation with 3α-Adiol G (23).

Our study confirms that the effects of isotretinoin on serum steroids are small and very unlikely to be of relevance to the suppression of sebum excretion or the resolution of acne, although isotretinoin decreases sebum excretion and normalizes hypercornification of the sebaceous ducts *in vitro* (24).

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