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TREATMENT OF ACNE WITH CYPROTERONE ACETATE AND ETHINYL ESTRADIOL

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Abstract. Tablets containing 2 mg cyproterone acetate and 0.05 mg ethinyl estradiol in a calendar package of 21 days were used as an oral contraceptive to treat acne. The series comprised 20 patients. The women were 18–43 years of age, and all had acne which had previously been resistant to therapy. The treatment was continued for 6 months. Serum testosterone, 17-OHCS, 17-KS, serum ALAT and gamma-GT were recorded prior to the treatment, at 3 and 6 months. Ten patients responded well to the treatment, 5 responded moderately well, 3 experienced no change, and 2 became worse. The serum testosterone level fell during the therapy and the ALAT level rose, though only one pathological ALAT value was recorded.

Animal experiments have shown that the function of the sebaceous gland is particularly dependent on androgens. Androgens stimulate the mitotic activity in the sebaceous glands, fibroblasts and hair follicles. Women with virilizing syndromes have been diagnosed for acne and hirsutism (1, 2, 9, 12). The beginning of acne is attributed to the elevation of the serum testosterone level at puberty (7). However, most acne patients have a normal serum testosterone level, and a majority of the patients do not have an increased secretion of 17-OHCS or 17-KS into the urine (6, 8).

The androgen metabolism of the skin has been postulated as a possible etiological factor in acne. Testosterone has been found to be reduced to dihydrotestosterone in the skin. Dihydrotestosterone is a more potent androgen than testosterone. The skin has been found to contain α-reductase enzyme and androgen receptor protein (1). The dihydrotestosterone content of the skin varies from site to site. In the diseased skin of acne patients it is 2–20 times greater than in the normal skin of control persons (10).

Estrogens probably cause a fall in the secretion of sebum only by reducing serum testosterone (9). Estrogens have not, however, yielded a sufficiently good therapeutic outcome in acne.

Attempts have been made to find an antiandrogen which could replace natural androgens in the receptors and thus eliminate the effect of natural androgens on the sebaceous gland. Wiechert synthesized a gestagen, cyproteroneacetate, in 1961. The preparation was found to have antiandrogenic properties (14, 15). It has been used to treat acne and hirsutism (1, 2, 15). At first the therapeutic doses were fairly large and side effects appeared. Cyproterone acetate can be combined with ethinyl estradiol. This combination of gestagen and estrogen also prevents ovulation.

In the present work, a low dose combination of cyproterone acetate and ethinyl estradiol was used in the therapy of postpubertal acne of 20 women.

PATIENTS AND METHODS

There were 20 female patients, with a mean age of 25.7 years (range 18–43). All of them had suffered from acne since early puberty. Two patients had Rosacea-like acne (ages 33 and 43 years), one had cystic acne and the others ordinary acne with pustules on the face and some also in the upper back. Prior to the present therapy, the patients had been treated with various methods for years. The drugs used more recently were tetracycline in 11 cases, contraceptive pills in 3 cases, vitamin A-acid applied locally in 3 cases and other local treatment in 7 cases. All the patients menstruated regularly. One patient had mild hirsutism; no other signs of virilism were found.

METHOD

The preparation SH B 209 AB (Schering AG) was used in 28-day packs, each containing 21 tablets. Each tablet contained 2 mg cyproterone acetate as the gestagen and 0.05 mg ethinyl estradiol as the estrogen. One tablet was taken each day, starting on the first day of the cycle and continuing for 21 days, after which there was a pause of 7 days.

The treatment was continued for 6 months. The only local treatment consisted of an inactive basic unguent, Aqualan (Orion) containing emulsifiers, glycerol and water.

The patients received no antibiotics or other systemic treatment during this investigation.

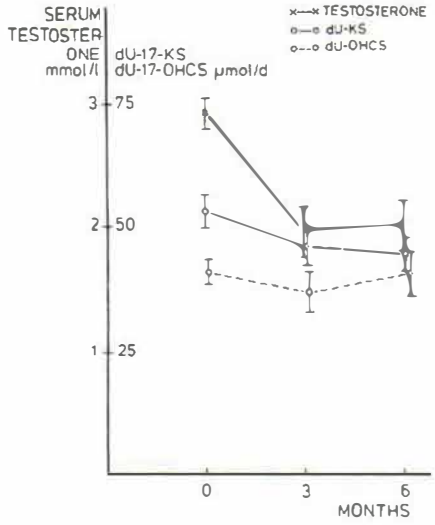

Fig. 1. Serum testosterone nmol/l (n=18), dU-17-KS and dU-17-OHCS mol/d (n=17) at 0, 3 and 6 months. n=the number of the patients from whom all three samples were collected. Mean±S.E.M.

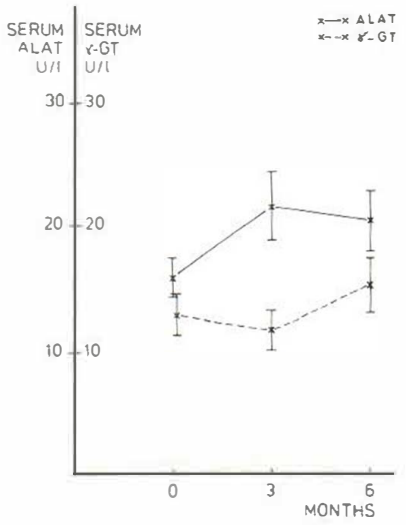

Fig. 2. Serum ALAT U/l (n=18) and serum γ-GT U/l (n=18). Mean±S.E.M. at 0, 3 and 6 months. n=number of the patients from whom all three samples were collected.

All patients underwent a gynaecological examination before and after therapy.

Before treatment, the patients were tested for serum testosterone, progesterone, estradiol, FSH, LH, prolactin and daily urine 17-OHCS and 17-KS. The functioning of the liver was tested by ALAT and γ-GT tests.

Before treatment, the plasma cortisol level was measured in all the patients at 8 a.m. and at 8 p.m., after which 2 mg dexamethasone was given and the cortisol level measured again at 8 a.m. the following morning.

Hormone determinations were carried out in the hormone laboratory of Oulu University Central Hospital. Plasma testosterone was assayed using the radioimmunoassay method described by Hammond et al. (5). Plasma testosterone, dU 17-OHCS and 17-KS, ALAT and γ-GT were measured 3 months and 6 months after the start of the treatment. The clinical condition was assessed by following the number of acne pustules, the inflammation of the area affected by acne, and the number of comedones. To facilitate objective assessment the patients were photographed before the treatment, and at 3 and 6 monthly intervals in check-ups after the treatment.

A condition in which almost all the papulopustulotic lesions had disappeared, with only a few remaining, was considered to constitute a good result. A condition in which about half of the lesions had improved was considered moderate. The same doctor examined the patients at each treatment session.

RESULTS

During the first 20 months of therapy the acne was aggravated in 4 of the patients. For this reason 2 of the 4 discontinued treatment, but the other 2 continued. The plasma testosterone values of the 2 patients who discontinued treatment were 3.13 and 2.95 nmol/l before treatment. Both had slightly elevated 17-●HCS secretion and one had slightly elevated 17-KS secretion. After 6 months the therapeutic outcome appeared good in 10 cases, moderate in 5, but poor in 3. The 2 patients with Rosacea-like acne were asymptomatic, and all the cysts of the one patient with cystic acne had disappeared. Seven of the patients with ordinary acne responded well to the treatment: only a few new pustules developed, either occasionally or just before menstruation. The enclosed colour photos show a good clinical course during the treatment.

So far, 12 patients have been followed up for 2 months after the discontinuation of therapy. The acne of 4 patients who showed good improvement has started to recur, but 3 patients are still asymptomatic.

Laboratory analyses

The plasma progesterone, estradiol, FSH, LH and prolactin levels measured before treatment

Clinical pictures of acne before and after 3½ and 6 months of treatment with cyproterone acetate and ethinyl estradiol. Good improvement of acne is seen.

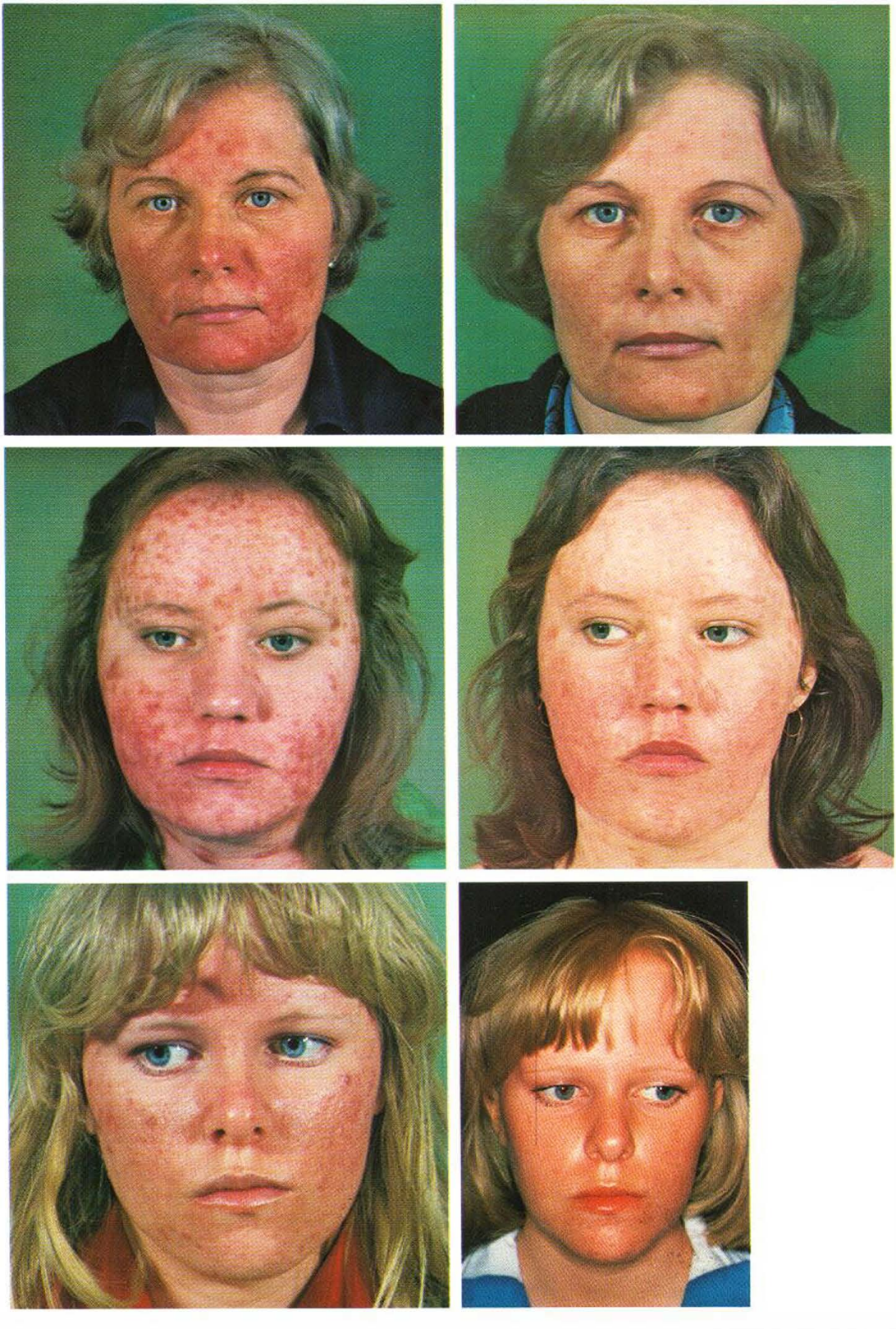

Table I. *The clinical data on serum testosterone, dU-17-OHCS and dU-17-KS during the investigation*

Normal value limits: testosterone 0.35–3.1 nmol/l, dU-17-OHCS 15–53 μmol/d, dU-17-KS 21–70 μmol/d. Pathological values are italicised.

		Testosterone nmol/l			17-OHCS μmol/d			17-KS μmol/d		
Pat	Age	Pre-treatment	3 month	6 month	Pre-treatment	3 month	6 month	Pre-treatment	3 month	6 month
1	43	2.3	1.03	1.41	37.9	27.7	22.1	45.1	39.3	18.7
2	30	*3.33*	2.85	1.58	41.6	*71.1*	52.3	62.4	40.6	39.9
3	18	2.6	0.75	1.79	35.6	30.9	23.4	63.0	43.2	47.7
4	36	2.13	2.3	2.31	*65.1*	39.0	47.7	*73.3*	62.4	57.2
5	26	2.06	0.99	1.03	38.3	30.5	40.3	32.4	37.8	38.7
6	33	2.4	0.85	1.26	20.8		45.1	23.3		45.1
7	20	*3.23*	*3.21*	2.95	35.9	26.0	27.8	54.3	41.6	44.7
8	27	2.6	1.2	1.94	27.8	*59.5*	*87.4*	56.6	59.5	65.5
9	18	2.8	1.41	1.08	34.6	26.0	31.2	54.1	26.6	45.8
10	33	2.4	*3.23*	2.07	34.0	41.3	45.1	44.8	43.7	39.5
11	18	*3.16*	1.41	1.08	34.6	26.0	31.2	54.1	29.6	45.8
12	20	*3.78*	2.24	1.65	44.3	30.3	23.4	56.2	29.2	17.2
13	18	*4.33*	2.4	2.6	43.7	23.6	45.8	59.4	52.1	48.0
14	20	2.95			*55.3*			60.6		
15	24	2.5	1.2	1.2	27.8	19.4	*62.5*	18.7	41.6	35.9
16	22	*3.61*	1.75	1.99	39.0	*75.0*	*62.5*	45.2	*97.3*	*73.4*
17	20	*3.715*	1.68	2.20	44.9	28.3	29.3	41.5	38.7	40.1
18	29	3.06	*3.64*	*5.74*	46.8	36.4	31.2	68.6	54.6	57.7
19	18	2.95	3.0	2.28	*58.7*	34.4	25.1	*70.4*	44.9	36.2
20	27	3.13			*53.1*			*89.9*		

corresponded to the phase of the menstrual cycle. The cortisol values in 2 patients taken at 8 a.m. (0.1 and 1.13 μmol/l) were slightly depressed. The plasma cortisol level fell normally by at least 25% in the evening and was less than 0.2 μmol/l 12 hours after the administration of 2 mg of desamethasone.

Table II. *Serum testosterone dU 17-KS, dU 17-OHCS: mean values and standard deviations*

The significances of the values were calculated by the paired *t*-test. *n* = the number of the patients from whom all three analyses were made

		Pre-treatment	3 month	6 month
Testosterone, nmol/l	Mean	2.94	1.95**	2.01*
	S.D.	0.58	0.90	1.05
	n	18	18	18
dU 17-KS, μmol/d	Mean	52.95	45.86	44.24
	S.D.	13.59	15.60	13.91
	n	17	17	17
dU 17-OHCS, μmol/d	Mean	40.62	36.79	40.49
	S.D.	9.44	15.87	17.35
	n	17	17	17

* $p<0.01$.
** $p<0.001$.

A significant fall in the plasma testosterone level was observed during the treatment, though in one patient the testosterone level rose during treatment, yet this patient's acne improved somewhat.

The mean serum ALAT level rose slightly, but only one pathological value was recorded.

There were no significant changes in the secretion of the steroids 17-KS and 17-OHCS into the urine during the treatment.

SIDE-EFFECTS

During the 6 months of therapy and thereafter the following side-effects attributable to the drug appeared:

Symptom	Number of patients
Weight gain less than	
1 kg	9/20
2 kg	6/20
3 kg	2/20
4 kg	0
Growth of breasts	5/20
Nausea	3/20
Depression (mild)	4/20

Decreased libido	1/20
Headache	2/20
Itching	2/20, the one ALAT ad 66
Growth of myoma	1/20 (age 43)
Initial increase of acne	4/20, two improved, two discontinued the treatment
Ovarian cyst (retention)	1/20
Shedding of hair after therapy	1/20
Folliculitis in the thighs	1/20

The 43-year-old Rosacea patient developed a myoma. She had pruritus and an ALAT value ad 66 u/l (normal range >40 u/l) at 3 months. The Rosacea improved greatly.

DISCUSSION

No ideal method for the treatment of acne has yet been found. Vitamin A-acid, long-term tetracycline therapy, benzoyl peroxide, cortisone injections into acne cysts, or oral contraceptives have all been unsuccessful in all cases of acne. We must therefore continue experimentation with new therapeutic methods and remedies.

Cyproterone acetate has previously been used in large doses. Fanta et al. (1976) used a preparation containing ethinyl estradiol in low-dosage treatment of 30 acne patients. Eighty-three per cent of their series responded well to this treatment. Cyproterone alone has caused disturbances of the menstrual cycle. The preparation used here gives rise to fewer side effects. In this study a good result of treatment was obtained in 50% of the patients and a moderate result in 25%. All the patients were suffering from relatively severe acne and none had responded to earlier treatment.

During the first weeks of the treatment the acne became worse in 4 of the 20 patients. This was considered to be an androgenic side effect of the preparation. Two patients who continued the treatment in spite of this improved greatly.

The significance of the plasma testosterone content as an aetiological factor in acne can be considered questionable. Nevertheless, modern hormone literature proposes that, e.g., the effect of certain oral contraceptives in increasing acne may be due to the fact that the gestagenic component of the oral contraceptive may displace testosterone from the sex hormon-binding globulin, resulting in an increase in the serum testosterone level (13). It was not possible in this work to determine the sex-hormone binding globulin.

We found a significant decrease in the plasma testosterone level during the treatment.

Ethinyl estradiol is known to reduce the serum testosterone level, even in men (11). It cannot, therefore, be assumed that the testosterone lowering effect of the preparation used is due solely to cyproterone acetate.

Numerous side effects appeared during the treatment, but none were serious. We feel, however, we can recommend that the treatment used here be tried on adult females whose acne has not responded well to other forms of treatment.

REFERENCES

1. Aydinlink, S. & Lacnit-Fixon, U.: Diane—eine Gestagen–Ostrogen Kombination mit Antiandrogenwirkung. Med Monatsschr *9:* 425, 1977.
2. Fanta, D., Neufeld, T., Sponsa, J. & Scheiner, W. H. F.: Die Anwendung von Antiandrogenen in der Behandlung der Akne. Wien Med Wochenschr 1977, in press.
3. Forchielli, E., Ras, G. S., Sarda, I. R., Gibree, N. B., Pocchi, P. E., Strauss, J. & Dorfman, R. I.: Effect of ethinyl-oestradiol on plasma testosterone levels and urinary testosterone excretion in man. Acta Endocrinol (Kbh) *50:* 51, 1965.
4. Förström, L., Mustakallio, K. K., Dessypris, A., Uggeldahl, P. E. & Adelcreutz, H.: Plasma testosterone levels in acne. Acta Dermatovener (Stockholm) *54:* 369, 1974.
5. Hammond, G. L., Viinikka, L. & Vihko, R.: Automation of radioimmunoassays for some sex steroids with use of both iodinated and tritiated ligands. Clin Chem *23:* 1250, 1977.
6. Hammerstein, J., Rossber, L., Moltz, L. & Zielske, L.: Use of cyproterone acetate in the treatment of acne, hirsutism and virilism. J Steroid Biochem *6:* 827, 1975.
7. Lee, P. A.: Acne and serum androgens during puberty. Arch Dermatol *112:* 482, 1976.
8. Lim, L. S. & James, V. H. T.: Plasma androgens in acne vulgaris. Br J Dermatol *91:* 135, 1974.
9. Pocchi, P. E. & Strauss, J. S.: Endocrinologic control of the development and activity of the human sebaceous gland. J Invest Dermatol *62:* 191, 1974.
10. Sansone, G. & Reisner, R. M.: Differential rates of conversion of testosterone to dihydrotestosterone in acne and in normal human skin. A possible pathogenetic factor in acne. J Invest Dermatol *56:* 366, 1971.
11. Smals, A. H. G., Kloppenborg, P. W. C., Lequin, R. M. & Benraad, J.: The effect of oestrogen administration on plasma testosterone, FSH and LH

levels in patients with Klinefelter's syndrome and normal men. Acta Endocrinol (Kbh) *77:* 765, 1974.
12. Strauss, J. S., Kligman, A. M. & Pocchi, P. E.: The effects of androgens and estrogens on human sebaceous glands. J Invest Dermatol *39:* 139, 1962.
13. Victor, A., Weiner, E. & Johansson, E. D. B.: Sex hormone binding globulin. The carrier protein for *d*-norgestrel. J Clin Endocrinol Metab *43:* 244, 1976.
14. Wiechert, R. & Neuman, F.: Gestagene Wirksamkeit von 1-Methyl- und 1–2-Methylen Steroiden. Arzneim Forsch *15:* 244, 1965.
15. Winkler, K. & Schaefer, H.: Das Verhalten des Talgsekretion während der Behandlung der Akne mit Cyproteronacetat und Äthinylöstradiol. Arch Dermatol Forsch *247:* 259, 1973.

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