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SEBO-SUPPRESSION BY COMBINED ANTI-ANDROGEN AND OESTROGEN IN FEMALE ACNE COMPARED WITH TETRACYCLINE

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Cyclic administration of a combination of cyproterone acetate and ethinyl oestradiol in 30 female acne patients led to a significant decrease of the cutaneous sebum excretion rate (SER) as assessed by the modified gravimetric technique. The mean percent reduction was 36.42±3.07 at the end of 6 months, and it remained reduced even after a treatment free period of 3 months. In comparison, tetracycline treated patients showed a slight rise in the SER that returned to near baseline values 3 months after cessation of the drug.

Key words : Sebo-suppression, Antiandrogen.

Although acne is a multifactorial disorder and endocrinal acne is known in Cushing's disease, congenital adrenal hyperplasia and polycystic ovarian syndrome, only recently has the role of androgens been clearly documented in the pathogenesis of adolescent acne.[1,2] Androgens mediate and control acne through their effect on the sebaceous glands.[3] This effect is reflected in the increased sebum excretion rate (SER) which serves as a traditional biochemical tool to monitor sebaceous gland function and correlates well with the clinical activity of acne.[4] The recognition of the role of androgens in the pathogenesis of acne opens an opportunity for hormonal therapy. Oestrogens are effective only in doses causing unacceptable side effects.[5] Oral contraceptives produce partial sebo-suppression but most of the modern pills contain only a small amount of oestrogen, with potentially androgenic progestagens which may exacerbate acne.[1] Thus, the most effective sebostatic agent seems to be a combination of oestrogen and the anti-androgen cyproterone (CPA). Herein, we report a quantitative sebum output study of female acne patients undergoing treatment with such a hormonal combination in comparison with long-term tetracycline.

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Materials and Methods

Sixty patients of moderate to severe acne with the ages ranging from 17 to 35 years (Mean 23.3 years) were studied. Patients receiving prior treatment with antibiotics, benzoyl peroxide and retinoic acid observed a drug-free period of one month before entering into the study. Patients were randomly allocated to two groups. Group I received combined cyproterone acetate (2 mg) and ethinyl oestradiol (50 μg) preparation (Diane—German Remedies) for 21 days beginning from the fifth day of menstrual cycle followed by a rest period of 7 days for a total period of six months. Group II was given oral tetracycline hydrochloride 500 mg twice a day for four weeks followed by 250 mg twice a day for five months. Pre-treatment assessment was done in all patients to exclude liver, renal and gynaecological disorders. Clinical evaluation was done by lesion counting, utilising an acne scoring system every month.[7] The scale used was, comedone-$\frac{1}{2}$, papule-1, pustule-2, nodules and infiltrates-3. Modified gravimetric technique was used to measure sebum excretion rate

(SER) before, at the end of six months and after a drug-free follow up period of 3 months. Patients were instructed to wash hairs and avoid cosmetics and oil before each procedure. Standard cigarette rolling absorbent papers (Capstan) were used to collect sebum at room temperature. All end-point weighings were performed on a sensitive electronic balance (Sartorius) and batches of control papers were kept for applying corrections. Paired t-test was applied to compare SER within the groups at different time intervals. Intergroup analysis was performed by independent t-test. Clinical lesion counts were projected into mean percentage reduction for better display.

Results

Only 24 patients of hormonal group and 22 patients of tetracycline group completed the study. A marked fall in the quantitative SER values was noticed in the patients undergoing hormonal therapy (2.99 ± 0.33 to 1.9 ± 0.26 microgram cm^{-2} min^{-1}) compared to a marginal rise during antibiotic treatment (2.62 ± 0.28 to 2.86 ± 0.27 microgram cm^{-2} min^{-1}) (Fig. 1). Repeat assessment of SER after a drug-free interval of 3 months showed a return to 2.56 ± 0.28 microgram cm^{-2} min^{-1} in hormonal group, the difference from the baseline values still remaining statistically significant ($p<0.001$). On the contrary, tetracycline group registered a return of SER to near baseline values. Intergroup comparison showed statistically significant difference only at the end of six months of therapy ($p<0.05$). Mean percentage reduction of total, inflamed and non-inflamed lesions demonstrated significant improvement at each month compared to the baseline acne scores. Intergroup analysis showed statistically significant improvement in the hormonal group at fourth, fifth and sixth months as compared to the antibiotic group ($p<0.001$). Patients undergoing tetracycline therapy relapsed with a greater rate after the cessation of therapy while improvement was persistently maintained in the anti-androgen group (clinical details, side effects and relapse data is under publication elsewhere.).

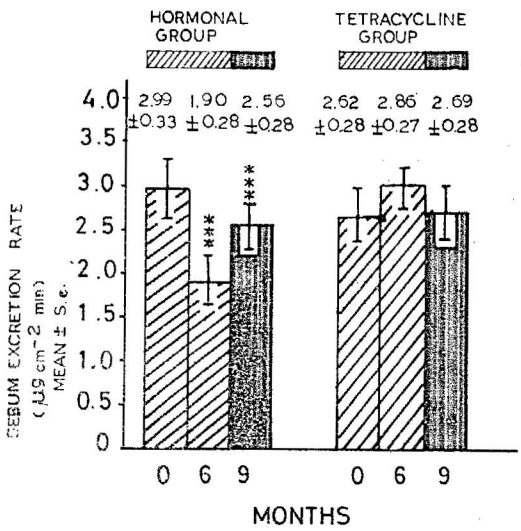

Fig. 1. Mean SER before and after treatment ($p<0.001$).

Comments

Ever since animal experiments demonstrated[9] the effect of cyproterone acetate on mouse sebaceous glands, various oral and topical anti-androgens have been tried. Cyproterone acetate is a competitive inhibitor of androgen receptors in the sebaceous glands and is most powerful of all.[10] Oral cyproterone acetate has been employed in variable doses of 5 mg to 100 mg daily leading to dose related sebo-static effect of 17 to 68%.[11-13] Administration of CPA alone could lead to menstrual irregularities and feminisation of male foetus. Therefore, its combination with oestrogen in the form of oral contraceptive to prevent pregnancy and achieve good cycle control is preferred. In addition, the combined drug has a cumulative action on the sebaceous glands, oestrogen acting by reducing the androgen synthesis by the central inhibition of gonadotropic secretion.[14] Studies on rats have also demonstrated a 35% reduction of SER by 5 mg/day CPA and 56% decrease by 2-4 mg/day oestradiol.[15] While CPA reduced

sebaceous gland mitoses and hence the size of the gland, oestradiol reduced intracellular sebum production. The combination of 5 mg ethinyl oestradiol and 2 mg cyproterone acetate has been reported to cause sebum suppression by 25 to 45.7%.[14,16] Recently, Miller et al[17] compared the sebo-suppression of an oral contraceptive containing norethisterone (1 mg) and ethinyl oestradiol (50 μg) with a combination of low dose CPA (2 mg), ethinyl oestradiol (50 μg) and high dose reverse sequential regime of CPA (50 mg) from days 5 to 14 and ethinyl oestradiol 50 μg from day 5 to 25. Marked reduction in sebum excretion rate was noticed in both anti-androgen groups. Our study shows a 36.42$\pm$3.07 mean percentage reduction of sebum output accompanied by the therapeutic supremacy of anti-androgen treatment. The reduced SER did not return to the baseline values even after 3 months of cessation of therapy and the clinical improvement was maintained as revealed by the persistently low acne scores. The marginal rise of SER in the tetracycline treated patients is probably due to the reduction of non-inflamed lesions leading to improved ductal sebum outflow as usually seen during benzoyl peroxide treatment. We conclude that anti-androgen cyproterone acetate and ethinyl oestradiol are powerful sebo-suppressors and more effective than usual tetracycline therapy. The combination treatment should be recommended to women having severe acne, recalcitrant to antibiotic therapy.

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