

Topical Cyproterone Acetate Treatment in Women With Acne

A Placebo-Controlled Trial

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Objective: To evaluate the clinical and hormonal response of topically applied cyproterone acetate, oral cyproterone acetate, and placebo lotion in women with acne.

Design: Placebo-controlled, randomized study.

Setting: Patients were recruited from the Institute of Endocrine Cosmetics, Vienna, Austria.

Patients: Forty women with acne.

Interventions: Treatment with oral medication consisting of 0.035 mg of ethinyl estradiol and 2 mg of cyproterone acetate (n=12), 20 mg of topical cyproterone acetate lotion (n=12), and placebo lotion (n=16) was offered. Patients were assessed monthly for 3 months.

Main Outcome Measures: Clinical grading according to acne severity and lesion counts as well as determinations of serum cyproterone acetate concentrations.

Results: After 3 months of therapy with topical cyproterone acetate, the decrease of mean facial acne grade from 1.57 to 0.67 was significantly better ($P<.05$) compared with placebo (which showed a change from 1.57 to 1.25), but not compared with oral medication (1.56 to 0.75) ($P>.05$). Lesion counts also decreased from 35.9 to 9.1 in the topical cyproterone acetate group compared with oral medication (45.4 to 15.5) ($P>.05$) and placebo (38.2 to 23.1) ($P<.05$). After topical cyproterone acetate treatment, serum cyproterone acetate concentrations were 10 times lower than those found after oral cyproterone acetate intake.

Conclusions: The therapeutic effect of topically applied cyproterone acetate for acne treatment was clearly demonstrated. Topically applied sexual steroids in combination with liposomes are as effective as oral antiandrogen medication in acne treatment, while reducing the risk of adverse effects and avoiding high serum cyproterone acetate concentrations.

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HORMONAL approaches to the treatment of acne have been the subject of much interest ever since the sebaceous gland was demonstrated to be sensitive to androgens. The use of topical antiandrogens has had theoretical appeal since the pilosebaceous unit was found to be an androgen-dependent structure. Unfortunately, however, this theory has not been translated into clinical practice.

17 β -Estradiol and progesterone have long been applied topically in the treatment of acne. The reasons for using topical rather than oral therapy include the avoidance of hepatic metabolism, the reduced risk of systemic adverse effects, the ability to combat acne in both female and male patients, and the lack of a contraceptive effect in women. It is known that cyproterone acetate is effective when given orally. However, trials using topical cyproterone acetate have not proved successful

because of the lack of a suitable vehicle for transdermal treatment.^{1,2} Cyproterone acetate is a potent steroidal antiandrogen with progestational activity. It is used alone or in combination with ethinyl estradiol or estradiol valerate in the treatment of women suffering from disorders associated with androgenization, eg, acne or hirsutism. Cyproterone acetate competes with dihydrotestosterone for the androgen receptor and inhibits translocation of the hormone receptor complex into the cell nucleus.³

This study was undertaken to consider once again a cyproterone acetate formulation delivered to the skin surface, thus approaching the target cell topically and bypassing the enterohepatic circulation. The aim of this open, placebo-controlled study was to compare the effectiveness of topical cyproterone acetate, an oral formulation containing 0.035 mg of ethinyl estradiol and 2 mg of cyproterone acetate (Dianemite, Schering, Vienna, Austria), and a placebo preparation in women with mod-

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PATIENTS AND METHODS

Forty-five women aged between 26 and 38 years (mean age, 30.3 years) with moderate to severe acne who consulted the endocrinology outpatient department for a hormonal evaluation and treatment of their acne were enrolled in this 3-month trial.

Informed consent was obtained from all the patients, and the study was approved by the local ethics committee. Patients with medical contraindications to the therapy or unwilling to smoke less than 5 cigarettes daily were not included in the study. Patients were required to use barrier contraception during the treatment period. All acne medication had been stopped 6 weeks before the commencement of the study.

During the initial visit, the patients were randomly assigned to 1 of the 3 treatment groups. One group (n=12) received an oral contraceptive regimen for 3 months, with administration of a daily dose of 0.035 mg of ethinyl estradiol and 2 mg of cyproterone acetate for the first 21 days of the menstrual cycle, followed by a 7-day pill-free interval. The first treatment cycle started on the first day of menstrual bleeding. The second group (n=12) used a topical cyproterone acetate lotion, with treatment starting on the first day of menstrual bleeding and being taken continuously for 3 months. The topical lotion was self-applied once daily in the evening, to the face only, with a calibrated pipette. The daily amount of cyproterone acetate liposome lotion used was 10 mL, containing 20 mg of cyproterone acetate. Liposome lotion consisted of soybean oil, eilecithin, glycerol, and oleic acid (Leopold Pharma, Graz, Austria).

The third group (n=16) used a placebo liposome lotion containing soybean oil, eilecithin, glycerol, and oleic acid without the active substance; it was applied as in the topical cyproterone acetate group.

Acne severity on the face was graded according to the method of Burke and Cunliffe,⁴ with the individual scores added up to yield a total result. Four sites on the face (chin, forehead, and left and right cheeks) were graded. The mean value from this grading was used for further calculations. In addition, numbers of macules, papules, pustules, nodules, and cysts on the face were counted by the same dermatologist (E.M.K.) at each visit. Lesion counts were defined as the total of comedones and inflammatory lesions. Only 3 of the patients had few inflammatory lesions, and their counts were thus added to the noninflammatory lesions. Acne on other parts of the body was not evaluated in this study. Assessments were done during the midpoint of the menstrual cycle, ie, between days 10 and 19, with day 1 being defined as the first day of menstrual bleeding. Before commencement of the trial, all patients underwent 2 baseline examinations performed 1 week apart. Progress assessments were made midway through the first, second, and third cycles of treatment. Forty women completed the trial, and their data were included in the final analysis. Five patients dropped out before the end of treatment.

TOPICAL APPLICATION OF CYPROTERONE ACETATE

The application system was similar to that used for topical 17 β -estradiol and topical 17 α -dihydrotestosterone studies. Pharmacokinetic details for these steroidal substances have been described previously.^{5,6} Because cyproterone acetate is a lipophilic steroid, a similar absorption rate was assumed. The daily transdermal cyproterone acetate dosage was 20 mg, based on a similar formulation combining soybean oil, eilecithin, glycerol, and oleic acid.

Liposomes were used to improve the transdermal penetration of the antiandrogen. Topical application of cyproterone acetate in patients with acne had been attempted before, but the clinical results were discouraging.

SERUM CYPROTERONE ACETATE LEVELS

Serum levels of cyproterone acetate were determined in 5 patients in the topical cyproterone acetate group both before treatment and 3 months after study entry, with blood samples taken exactly 45 minutes after the last topical cyproterone acetate application. Baseline serum cyproterone acetate concentrations were below the detection limit. Serum cyproterone acetate levels were measured by radioimmunoassay, by a dextran-coated charcoal method. Aliquots of serum (0.1 mL) were diluted with physiological saline to a final volume of 0.5 mL. After extraction with 2.5 mL of diethyl ether, the ether phase was separated and fully evaporated, and the residue was reconstituted with 0.8 mL of an assay buffer. This solution was incubated with 0.1 mL of tritiated cyproterone acetate (specific activity, 0.84 GBq/mg; Schering AG, Berlin, Germany) and 0.1 mL of antiserum (batch C003, Schering AG) at 4°C for 16 hours, mixed with 0.2 mL of dextran-coated charcoal, and vortexed. After 15 minutes at 4°C, the mixture was centrifuged. The supernatants were decanted into liquid scintillation vials and mixed with 4.5 mL of scintillation cocktail. The radioactivity was measured on a scintillation counter. To obtain the standard curves, 1 mg of cyproterone acetate was dissolved in methanol and diluted with assay buffer, yielding final concentrations ranging from 39 to 10 000 pg/mL. In addition, a drug-free sample (0 pg/mL) was used. Calibration and samples were analyzed in duplicates. A spline function was used for the evaluation of the data. The interassay and intra-assay coefficients ranged from 5.0% to 13.0%. The mean blank value for blank control samples was found to be 28 pg/mL.

STATISTICAL METHODS

Overall significance of the group effect was evaluated by analysis of variance. Pairwise comparisons between groups were made by Student *t* tests for mean comparison. A *P* value less than .05 was considered to indicate significance. The program used for statistical analysis was SAS/PROC GLM (SAS/STAT software, version 6, SAS Institute Inc, Cary, NC, 1989).

erate to severe acne. Moreover, we evaluated in a preliminary study the serum cyproterone acetate levels after transdermal application and compared them with levels obtained by administration of an oral preparation containing 0.035 mg of ethinyl estradiol and 2 mg of cyproterone acetate.

RESULTS

Of the 45 patients who entered the study, 40 completed the 3 cycles of treatment and were included in the analysis (12 receiving oral cyproterone acetate, 12 receiving topical cyproterone acetate, and 16 receiving

Table 1. Clinical Features of Patients in the Trial

Therapy	No. of Patients Entering Trial (No. Completing)	Mean (Range)									
		Age, y	Weight, kg	Facial Acne Grade				Lesion Count			
				Baseline	1 mo	2 mo	3 mo	Baseline	1 mo	2 mo	3 mo
Oral cyproterone acetate	14 (12)	29.4 (26-37)	58.2 (55.7-61.4)	1.56 (1.55-1.58)	1.22 (1.18-1.24)	1.15 (1.12-1.17)	0.75 (0.20-0.97)	45.4 (30-58)	33.5 (21-42)	24.8 (16-35)	15.5 (11-21)
Topical cyproterone acetate	13 (12)	31.3 (26-38)	63.1 (55.3-77.3)	1.57 (1.56-1.58)	1.16 (1.10-1.18)	1.12 (1.10-1.15)	0.67 (0.59-0.80)	35.9 (28-59)	21.8 (12-40)	17.7 (9-33)	9.1 (3-20)
Placebo	18 (16)	30.3 (26-38)	67.0 (55.1-77.5)	1.57 (1.54-1.59)	1.39 (1.30-1.45)	1.30 (1.28-1.40)	1.25 (1.22-1.28)	38.2 (29-47)	32.4 (25-42)	27.6 (21-35)	23.1 (17-30)

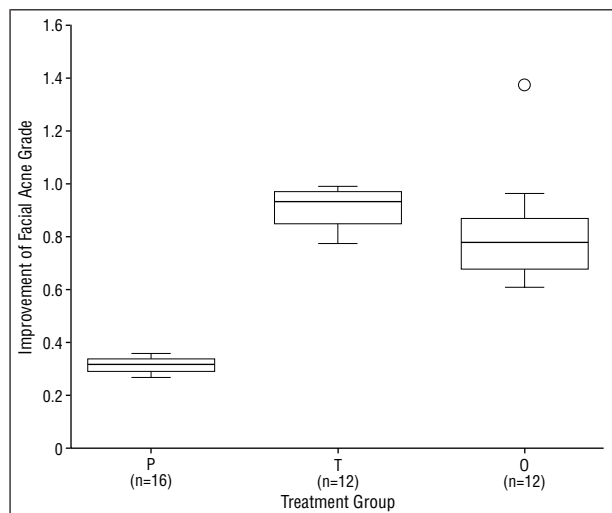


Figure 1. Boxplot of response of the 3 treatment groups in facial acne grades during 3 months of treatment. Mean values (ranges) are as follows: group T, 0.90 (0.77-0.99); group O, 0.81 (0.61-1.37); and group P, 0.32 (0.27-0.36).

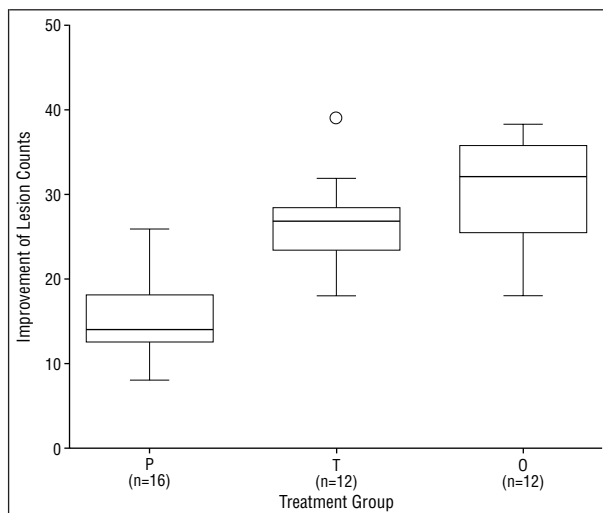


Figure 2. Boxplot of response of the 3 treatment groups in lesion counts during 3 months of treatment. Means (ranges) are as follows: group T, 26.8 (18.0-39.0); group O, 29.9 (18.0-38.0); and group P, 15.1 (8.0-26.0).

placebo). Two patients in the oral cyproterone acetate group dropped out of the study because they had failed to take the tablets regularly. One patient was excluded from the topical cyproterone acetate group because of a moderate local reaction and because she was not willing to use the mechanical contraception. Two patients in the placebo group withdrew from the study for personal reasons. The patients' ages, their initial mean acne grades, and lesion counts are listed in **Table 1**.

Response to therapy was measured by calculating the difference between baseline measurements and measurements after 3 months of therapy. During the 3-month assessment period, both oral and topical cyproterone acetate were found to be significantly more effective than the placebo preparation in reducing mean facial acne grades and lesion counts ($P < .05$ for both groups). No significant differences in treatment success were observed between the oral and topical therapy ($P > .05$) (**Figure 1** and **Figure 2**).

After 3 months of topical cyproterone acetate application, lesion counts had decreased from a mean of 35.9 (range, 28-59) to 9.1 (3-20) ($P < .05$). The serum levels of cyproterone acetate are shown in **Table 2**. Serum cyproterone acetate concentrations were below the detection limit of 28 pg/mL before the treatment but increased to values of between 119 and

Table 2. Serum Cyproterone Acetate Levels Before and After Topical Cyproterone Acetate Therapy in 5 Patients

Patient No./ Age, y	Serum Cyproterone Acetate, pg/mL	
	Before Treatment	After 3 mo of Treatment
1/34	<28*	226
2/37	<28	281
3/26	<28	286
4/35	<28	311
5/30	<28	119

*Detection limit.

311 pg/mL after topical cyproterone acetate application. No subjective adverse effects or bleeding irregularities were observed in either of the groups during the 3 months of treatment.

COMMENT

Acne is a common disorder in young females and males, and the therapeutic strategies available at the moment are not always sufficient and without shortcomings. Therefore, there is still a need for more effective topical therapies, particularly those that are free of harmful ad-

verse effects and easy to handle. There are numerous well-established hormonal and nonhormonal approaches to the treatment of acne. As acne is known to be an androgen-dependent disorder, oral antiandrogen treatment has been shown to be successful. In the present study, we assessed the efficiency of topical cyproterone acetate in patients afflicted with acne. Although the number of subjects in this study was small, patients were specifically selected from a large group of patients with acne on the basis of having moderate to severe lesion scores, and no other visual evidence of hyperandrogenism. Moreover, none of the patients had received any systemic treatment for 6 weeks before the commencement of the study.

THE USE OF topical antiandrogens in the treatment of acne has been intensively investigated ever since the pilosebaceous unit was found to be androgen dependent. In 1969, Cunliffe et al¹ used topical cyproterone acetate dispensed in dimethyl sulfoxide in 12 patients but found no improvement because of the lack of a suitable vehicle for the steroids. Seven years later, Pye et al² used 1% cyproterone acetate suspended in cetomacrogol cream BPC (formula A), but none of the patients showed any marked acne improvement. Meanwhile, a wealth of experience in the area of acne treatment has been gained by various clinicians and researchers. There are several alternatives to cyproterone acetate. Estrogens, progesterone, spironolactone, flutamide, and gonadotropin-releasing hormone analogues have all been used in various concentrations in clinical trials.⁷⁻⁹ These substances reduce sebaceous gland activity leading to a clinical improvement of acne. However, they have 1 problem in common. They are ingested and thus affect the entire human organism, producing systemic adverse effects.

It is well known that oral estrogens effectively suppress sebum excretion and improve acne in both men and women. However, the doses required to produce a therapeutic effect are associated with unacceptable adverse effects.¹⁰ The effect of topical progesterone also has been evaluated; whereas a reduction in the sebum excretion rate was demonstrated in female patients, no change was seen in male patients. Moreover, the sebosuppressive effect was lost after 3 months.¹¹

Antiandrogens show the most likely source of therapeutic success in the hormonal manipulation of the sebaceous gland.¹² Cyproterone acetate is most often prescribed in combination with ethinyl estradiol, with the maximum clinical effect generally seen between the third and sixth months of treatment. Oral spironolactone also has been shown both to decrease sebum excretion rates and to improve clinical acne.¹³ However, the prescription of spironolactone in this indication has been markedly reduced since the publication of animal research data indicating that it may cause breast cancer in rats.¹⁴ The oral nonsteroidal antiandrogen flutamide has been found to reduce acne but it is not suitable for clinical use.¹⁵ Chlormadinone acetate is a 19-norprogesterin with antiandrogenic properties. It is

used in combination with ethinyl estradiol as an oral contraceptive and has proved to be successful in cases of mild acne and seborrhea.¹⁶ Dienogest, apparently the first 19-nortestosterone derivative with antiandrogenic effects, is currently used in oral contraceptives and has been suggested for antiandrogen treatment. However, clinical trials evaluating the antiandrogen property of this substance are inadequate.¹⁷

Finally, the new topical nonsteroidal antiandrogen inocoteron acetate has produced only modest clinical effects in the treatment of acne.¹⁸ Evidence suggests that not all patients with acne exhibit elevated serum androgen levels.¹⁹ Rather, several studies have indicated an increased local formation of androgens, disturbances of the androgen metabolism,²⁰ or an increased sensitivity of the androgen receptor to normal levels of androgens.²¹ Consequently, antiandrogens and 5 α -reductase inhibitors may also play a role in the treatment of clinically hyperandrogenic women.²²

Despite the lack of success with topical cyproterone acetate in previous studies, we undertook a placebo-controlled trial using a liposome lotion as a carrier for cyproterone acetate to overcome the difficulty of delivering the active substance to the target cell. In the present study, the therapeutic effectiveness of topically applied cyproterone acetate in cases of acne was clearly demonstrated. Mean facial acne grades and lesion counts decreased significantly with both topical and oral cyproterone acetate. The preliminary serum determinations confirmed our initial expectation that topical use would result in lower serum cyproterone acetate levels than would oral cyproterone acetate intake. In fact, cyproterone acetate levels were 10 times lower after topical than after oral application, while producing a similar clinical response. According to data in the literature, cyproterone acetate levels after oral intake of 2 mg of cyproterone acetate can be expected to be an order of magnitude higher (4073 pg/mL); however, this is because a contraceptive effect is required.²³ Further studies and pharmacokinetic investigations are necessary to determine the optimal dosage and carrier regimens.

The mechanisms responsible for the effectiveness of topical cyproterone acetate are outside the scope of the present study. Whether topical cyproterone acetate acts directly on the skin or whether the serum levels, although low, are responsible for its therapeutic effects will have to be determined in further studies.

Notably, a significant therapeutic improvement compared with the placebo group was seen after only 3 months of treatment with both oral and topical cyproterone acetate. In summary, the results of this study suggest that topical application of the antiandrogen cyproterone acetate in the treatment of acne is as effective as oral cyproterone acetate in combination with ethinyl estradiol, provided that a suitable carrier is used. The liposome lotion we used unlocks the potential of topical cyproterone acetate application and releases the benefits of reduced adverse effects, at least within the treatment period evaluated in this study. Thus, the cyproterone acetate lotion represents a suitable alternative or additional local treatment for women with acne.

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