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Effects on Acne of Two Oral Contraceptives Containing Desogestrel and Cyproterone Acetate

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ABSTRACT: **Objective**—To compare the effects of a low-dose oral contraceptive containing desogestrel (Marvelon) and an anti-androgenic preparation containing cyproterone acetate (Diane) in Oriental women suffering from acne. **Methods**—In an open-label, bi-center, randomized study, 32 women using Marvelon® and 34 using Diane® were followed for 6 treatment cycles. The measured variables were objective and subjective severity of acne, and related biochemical variables such as sex hormone-binding globulin and free and total testosterone. **Results**—In Center A, with both preparations a decrease in mean objective acne score was observed, reaching statistical significance with Diane ($P < .05$). In addition, there was a significant between-group difference at cycle 6 ($P < .05$). In Center B, a consistent and significant decrease in mean acne score was observed with Marvelon after three and six treatment cycles ($P < .05$ and $P < .01$) and with Diane after six treatment cycles ($P < .001$). There were no significant between-group differences. The decrease in percentage of severe/moderate acne was statistically significant with Marvelon in Center B ($P = 0.002$) and with Diane in Centers A ($P = 0.014$) and B ($P = 0.004$). Both preparations increased plasma levels of sex hormone binding globulin and seemed to decrease those of total and free testosterone, but no statistically significant relationships between acne severity and biochemical variables could be detected. **Conclusion**—Both Marvelon and Diane are effective in the treatment of acne in Oriental women who also need reliable contraception, without marked differences between the preparations. *Int J Fertil* 41(4):423–429, 1996

KEY WORDS: contraceptives, desogestrel, cyproterone acetate, acne, efficacy, sex hormone binding globulin, testosterone

INTRODUCTION

ACNE VULGARIS IN WOMEN USUALLY starts to develop with adrenarche, and its severity usually declines after puberty. It has been reported that up to 30% of teenagers develop acne of sufficient severity to require medical treatment. Androgens increase sebaceous gland size and sebum production, whereas estrogens decrease sebum production by suppressing pituitary gonadotropin secretion as well as ovarian and adrenal androgen secretion. Estrogens also increase hepatic synthesis of sex hormone-binding globulin (SHBG), resulting in increased SHBG plasma levels. In contrast, androgens, as well as progestogens with intrinsic androgenic activity, reduce SHBG plasma concentrations. SHBG plays an important role in binding circulating androgens, thereby decreasing free androgen concentrations [1].

Combined oral contraceptives (OCs) have been implicated in both the pathogenesis and treatment of acne: estrogen-dominant preparations may induce improvement of preexisting acne [2–5], whereas androgen-dominant OCs, particularly those containing l-norgestrel, have been reported to be associated with exacerbation of acne and even with triggering the development of acne [4–7].

Desogestrel, a gonane progestogen with low intrinsic androgenic activity, and cyproterone acetate, an anti-androgen from the pregnane group, with weak progestogenic activity, are both used as the progestogenic component in combined OCs. Cyproterone acetate-containing preparations are also used in various countries for treatment of androgenic (skin) disorders. Because of the absence of androgenic effects with desogestrel- and cyproterone acetate-based OCs, they are both suitable for use by women who suffer from acne and/or hirsutism and who also need reliable, reversible contraception.

The clinical efficacy of both preparations, whether used in OCs or in the treatment of acne, is well established with regard to women in Western countries. However, how these preparations would perform as anti-acne treatment for Asian women is largely unknown. In addition, it is not clear whether the changes in acne severity with use of OCs are correlated with the changes in biochemical variables, such as SHBG and total and free testosterone (T). The main objective of our study

was to compare the efficacy in acne treatment of Oriental women of an OC preparation containing desogestrel and an anti-androgenic preparation containing cyproterone acetate.

METHODS

Design

This randomized, bi-center, open-label, comparative study with a duration of 6 treatment cycles was performed in two centers in Thailand: the Prince of Songkhla University in Songkhla (Center A; 17 women on desogestrel and 19 on cyproterone acetate) and the Rajvithi Hospital in Bangkok (Center B, 15 women on desogestrel and 15 women on cyproterone acetate). Before entering the study all subjects had given voluntary, informed consent. The study was conducted in compliance with both the Declaration of Helsinki and local rules and regulations, as well as local ethical standards.

Selection of Subjects

Subjects eligible for inclusion were women who had a wish to use OCs, presenting with acne, between 16 and 30 years of age, and willing to give their informed consent. Exclusion criteria were contraindications to the use of OCs, current use of systemic treatment for acne, delivery or abortion within the last 6 months, breastfeeding within the last 3 months, treatment with other OCs or treatment with injectable contraceptives in the last 3 months. Subjects were withdrawn from the study if contraindications to OCs use developed, or if disease occurred making further participation in the study impossible or unethical.

Study Drugs and Dosage Instructions

Eligible subjects were randomized to one of the following two study medications: (1) 150 µg desogestrel plus 30 µg ethinyl estradiol (Marvelon®, N.V. Organon, Oss, the Netherlands) for oral administration; (2) 2,000 µg cyproterone acetate plus 50 µg ethinyl estradiol (Diane®, Schering AG, Berlin, Germany) for oral administration.

The study consisted of a baseline cycle in which no study medication was taken, and six successive treatment cycles. Dosage instructions were similar

for both study medications: following the baseline cycle, the first tablet was taken on the first day of menstruation. Tablets were to be taken for 21 consecutive days, followed by a 7-day tablet-free interval. The same dosage schedule was used in the subsequent five treatment cycles.

Procedures and Evaluation Methods

After enrollment into the study, during the baseline cycle the subjects were checked for inclusion and exclusion criteria and medical history was taken; a medical examination, including measurement of blood pressure, and a gynecological investigation were performed. During this baseline cycle the severity of acne was rated. The acne rating in both centers was performed semi-quantitatively by counting the number of facial comedones, papules, and pustules. In addition, in Center A the number of nodulocystic lesions was also recorded. Acne severity was rated as follows:

absent (acne score = 0):	no acne at all
mild (acne score = 1):	≤15 comedones + ≤10 papules + ≤5 pustules
moderate (acne score = 2):	>15 comedones or >10 papules or >5 pustules and <5 nodulocystic lesions
severe (acne score = 3):	≥5 nodulocystic lesions

In addition to this semi-quantitative method of acne rating, a subjective impression of acne severity by the patients themselves was also recorded during each visit. However, the two study centers employed different methodologies for the subjective assessment of acne. In Center A, patients were asked about the possible change from baseline in the severity of acne. The possible answers from which to choose were "cured", "improved," "no change," and "worse." In Center B, though, the patients were asked how they regarded their acne severity at the time of the visit. The possible answers here were "absent," "mild," "moderate," and "severe."

In addition to semi-quantitative and subjective acne rating, blood was drawn for assessment of biochemical variables (SHBG, free T, total T). After blood collection, the samples were stored at -20°C

for analysis at the biochemical research and development laboratories of N.V. Organon in Oss, the Netherlands. Laboratory variables were assessed by previously published methods [8].

Subsequent clinic visits were scheduled after one, three and six treatment cycles. During each of these visits, the severity of acne was rated both objectively and subjectively and a medical examination was performed. During cycles 3 and 6 blood samples were drawn for the assessment of biochemical variables.

Statistical Analysis

For each of the treatments the changes in semi-quantitative acne score over time were analyzed by the Wilcoxon test for paired observations. These changes were also compared between both groups by means of a Wilcoxon two-sample test. To investigate trends in the percentage of patients with moderate/severe acne over time, the chi-square trend test of van Eeden and Hemelrijk [9] was used. A logistic regression analysis was done to investigate the relationship between the severity of acne (percentage moderate/severe) and the blood values at baseline. The changes in blood values after 3 and 6 months were compared with the change in acne score (equal or decreased) after 3 and 6 months using Student's *t* test.

Because the number of nodulocystic lesions was not systematically recorded in Center B, an acne score of 3 (severe) could usually not be checked. In view of these fundamental between-center differences in scales for rating the severity of acne, it was decided to perform separate statistical analyses for each of the centers.

RESULTS

Subject Characteristics

Analysis of the demographic characteristics of the study groups revealed that they were comparable with respect to mean age, age at menarche, parity, body weight and blood pressure. At baseline no statistically significant differences were observed between preparations or between centers. Although 11 subjects were over 30 years of age (the maximum age according to the protocol), it was decided not to exclude them from the analyses.

Effects on Acne

The semi-quantitative mean acne scores with Marvelon and Diane at baseline and after one, three, and six treatment cycles are presented for both centers in Figures 1 and 2.

In Center A, with Marvelon the decrease in mean semi-quantitative acne score did not reach statistical significance, whereas with Diane the decrease reached statistical significance after 3 and 6 treatment cycles ($P < .05$). In addition, there was a statistically significant difference in the change in acne scores between both groups at cycle 6 ($P < .05$). In Center B with both preparations a consistent decrease in mean acne score could be observed, and was statistically significant with Marvelon after 3 and 6 treatment cycles ($P < .05$ and $P < .01$, respectively), and with Diane after 6 treatment cycles ($P < .001$). There were no significant between-group differences in Center B.

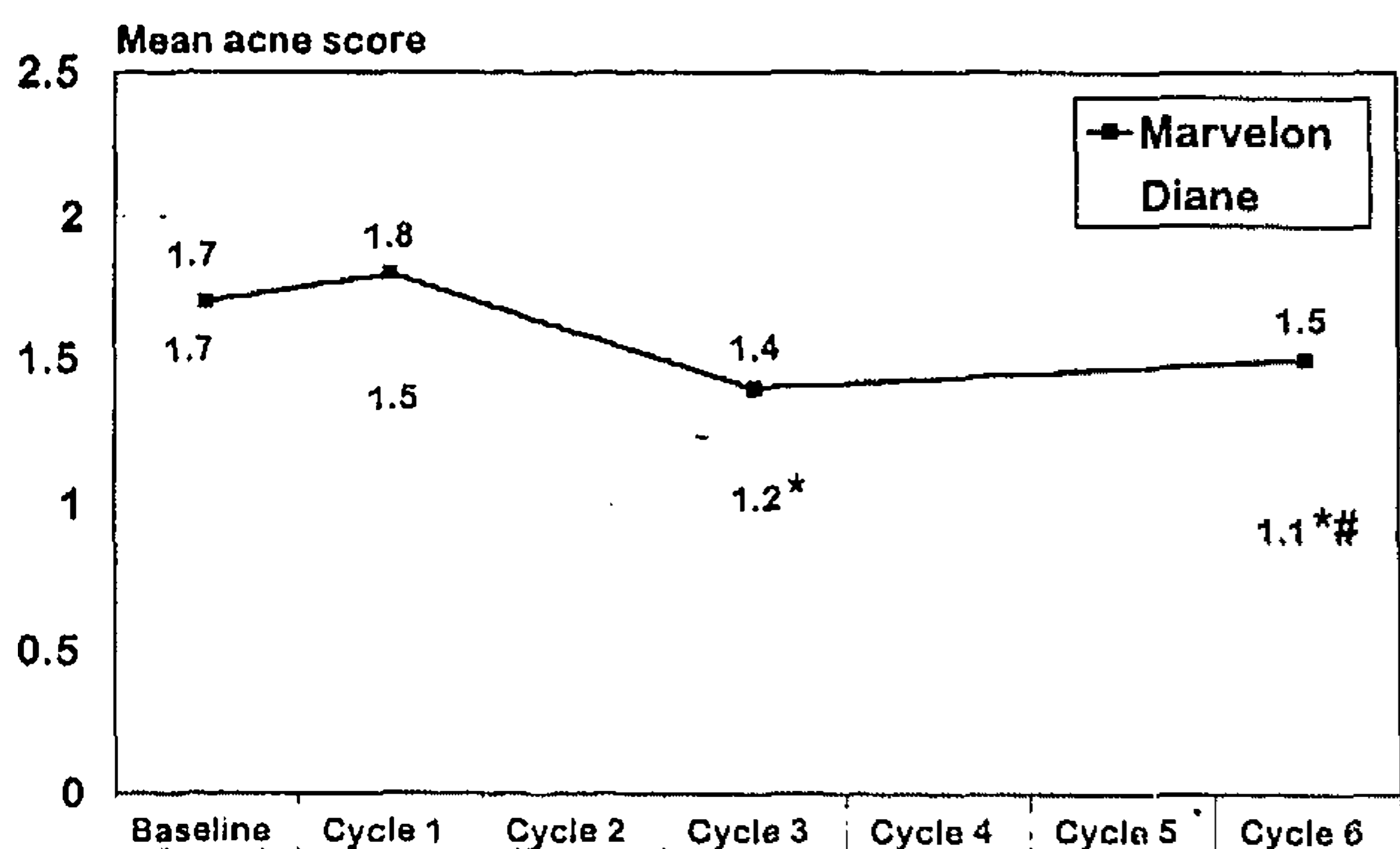


FIG. 1. Mean acne score in Center A. * $P < .05$ vs. baseline; # $P < .05$, Marvelon vs. Diane.

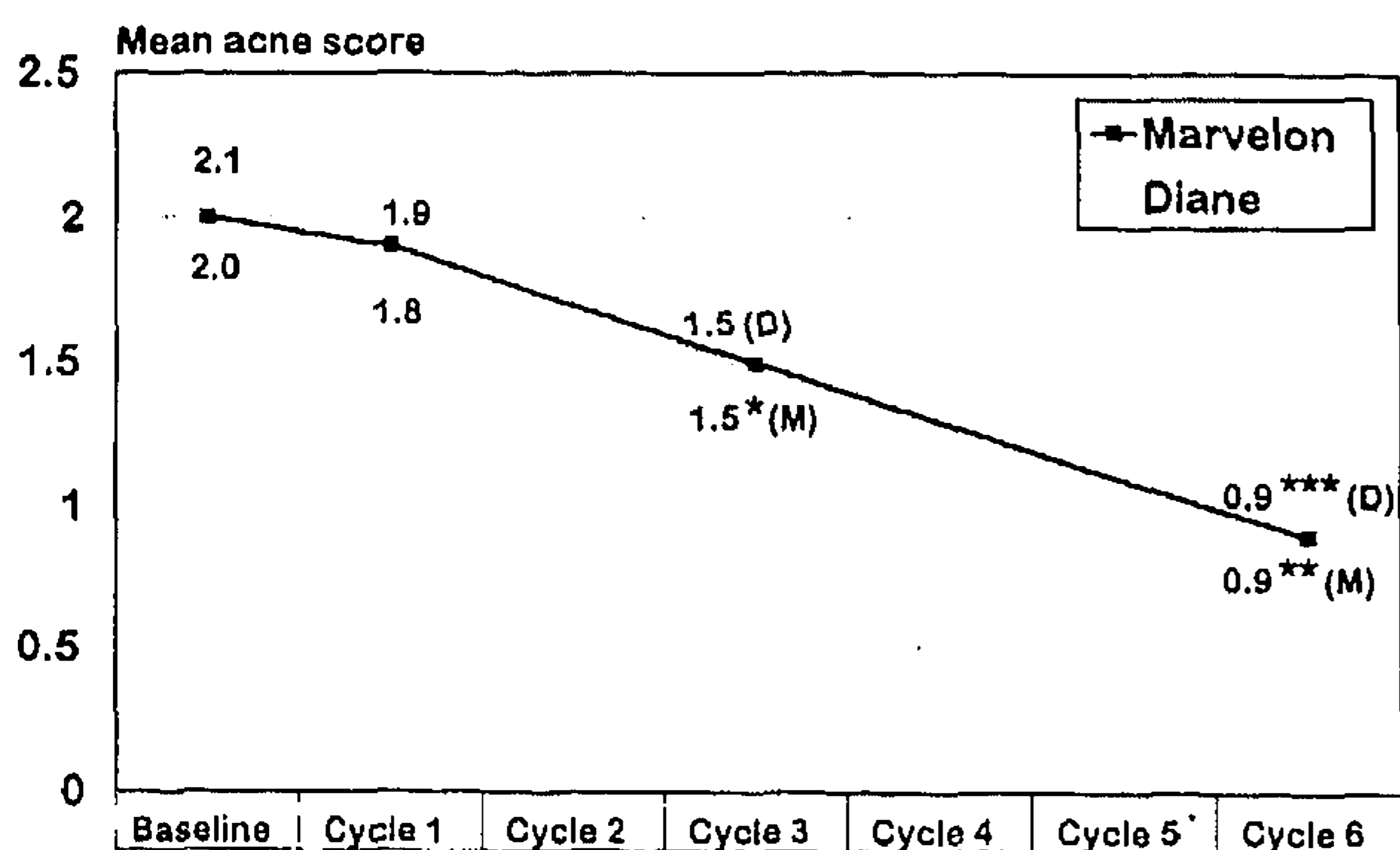


FIG. 2. Mean acne score in Center B. * $P < .05$, ** $P < .01$, *** $P < .001$ vs. baseline.

The change in the percentage of patients with moderate/severe acne score per treatment group and per center was tested with the trend test of van Eeden and Hemelrijk [9]. In Center A, the percentages of subjects with moderate/severe acne at baseline and during cycles 1, 3, and 6 with Marvelon were 53%, 50%, 36%, and 43%, which did not reach statistical significance for trend ($P = 0.64$), whereas with Diane the corresponding percentages were 63%, 44%, 18%, and 12%, a change statistically significant for trend ($P = 0.014$). In Center B, the percentages of subjects with moderate/severe acne for Marvelon were 100%, 93%, 50%, and 0%—statistically significant for trend ($P = 0.002$); for Diane these percentages were 100%, 80%, 50%, and 7%, also statistically significant for trend ($P = 0.004$). There were no statistically significant trend differences between the two preparations in either center.

After six treatment cycles the objective acne scores had decreased in about 50% of subjects in Center A and in almost all subjects in Center B (data not shown). There was no statistically significant difference in the percentage of patients with a decrease in acne score between the two treatment groups (chi-square-test, Center A: $P = 0.89$; Center B: $P = 0.37$).

The subjective acne scores in this study were in line with the semi-quantitative measurements as presented earlier, since the patient's opinion concerning the effect on acne usually followed the changes that were reported after objective judgement. In Center A, of the 14 subjects in the Marvelon group who completed the study, 13 had noted a subjective improvement, whereas one subject felt that there had been no change in her acne status. Of the 17 who completed the study in the Diane group, 14 considered the acne either cured (1) or improved (13), whereas the remaining three subjects reported no change from baseline. In Center B, a similar observation was made: at baseline all 15 subjects in the Marvelon group considered their acne as being either moderate (9) or severe (6), whereas after six treatment cycles all 12 remaining subjects considered their acne as absent (10) or mild (2). In the Diane group the same trend was observed: at baseline all 15 subjects considered their acne as moderate (6) or severe (9), whereas at the end of the study all 14 remaining subjects considered their acne as being either absent (9) or mild (5).

TABLE I
Effects on biochemical variables with Marvelon® and Diane® per cycle (mean ± SE).

Variable	Center A			Center B		
	Baseline	Cycle 3	Cycle 6	Baseline	Cycle 3	Cycle 6
SHBG (nmol/L)						
Marvelon	95.0 ± 14.8	159.0 ± 13.4‡	155.0 ± 15.8†	51.1 ± 7.5	144.8 ± 22.2†	142.2 ± 12.5‡
Diane	83.2 ± 8.1	181.2 ± 14.2‡	175.3 ± 16.1‡	65.5 ± 7.1	203.8 ± 24.0‡	188.2 ± 33.9†
Total T (nmol/L)						
Marvelon	2.33 ± 0.44	1.67 ± 0.44*	1.60 ± 0.44*	2.47 ± 0.26	1.49 ± 0.23†	1.67 ± 0.28†
Diane	2.21 ± 0.32	1.35 ± 0.29‡	2.18 ± 0.44	2.37 ± 0.27	1.76 ± 0.27*	1.88 ± 0.29
Free T (pmol/L)						
Marvelon	10.51 ± 1.83	5.98 ± 1.02†	6.48 ± 1.08*	4.07 ± 0.70	2.24 ± 0.43‡	2.41 ± 0.48†
Diane	8.72 ± 0.95	5.29 ± 0.80†	7.52 ± 1.11	3.05 ± 0.33	2.04 ± 0.32†	2.40 ± 0.24

* $P < .05$, † $P < .01$, ‡ $P < .001$ vs. baseline. T = testosterone.

Effects on Biochemical Variables

The effects of the two treatments on plasma levels of SHBG, total T, and free T are presented in Table I. After three and six treatment cycles, in both study centers Marvelon and Diane induced a statistically significant increase in SHBG plasma levels ($P < .01$). Although there was a decrease in plasma levels of both total and free T with both preparations, after six cycles the changes only reached statistical significance with Marvelon ($P < 0.05$). There were no statistically significant differences between the preparations, and there were no correlations between the changes in acne score and the changes in biochemical variables (data not shown).

Drop-outs

Of the 66 enrolled subjects, six in the Marvelon and three in the Diane group did not complete the study. The reasons for drop-out in the Marvelon group were: severe headache/dizziness (1), weight gain (1), loss to follow-up (2), and migration (2). In the Diane group, subjects dropped out because of severe headache/dizziness (1), and unknown reasons (2).

DISCUSSION

In this study, both Marvelon and Diane were effective in treatment of acne, without marked differ-

ences between the preparations. One of the causes for a between-group difference in mean acne score at cycle 6 in Center A might well be chance, since the difference only reached borderline significance ($P = 0.038$), whereas all other differences in Centers A and B between Marvelon and Diane were not statistically significant. The small groups at each treatment center as well as the between-center differences in acne rating methodology may have played a role here.

During use of Marvelon or Diane, plasma concentrations of SHBG usually increase by about 200%, since this estrogen-dependent effect is not counteracted by the intrinsic androgenicity of the progestogenic component in these OCs. The increase of SHBG results in an increased protein binding of plasma T, thereby reducing the free plasma T concentration. It is thought that the plasma concentrations of free (and therefore active) T are correlated with the severity of acne [10]. The decrease in free plasma T concentration as observed in most studies with Marvelon and Diane may therefore influence acne symptoms favorably [8,11], although in this study no correlation between changes in severity of acne and changes in biochemical variables could be found.

In two Phase IV studies with 11,605 [12] and 1,958 [13] subjects, the use of Marvelon has been shown to improve subjectively rated pre-existing acne in 42–75% of women after six cycles of use,

depending on the severity of symptoms (improvement seemed to be better with mild and moderate acne than with severe acne). In another open study in hyperandrogenic adolescents with moderate or severe facial and body acne, Marvelon induced an improvement in acne symptoms in all subjects during treatment, with a complete disappearance of symptoms in 90% of the subjects after 1 year of treatment [14]. It must be noted here, however, that the study by Bilotta and Favilli [12] was not especially designed to demonstrate efficacy on acne, and valid conclusions should preferably be drawn from well-controlled studies specially designed to investigate the effect of OCs on acne.

In a 6-cycle controlled study investigating the effect of OCs on acne, Marvelon increased SHBG and decreased free T plasma concentrations, with a statistically significant improvement of acne symptoms when compared with pretreatment. In addition, this improvement was statistically significantly better than with a levonorgestrel-containing OC [15], as measured by the modified photographic acne rating method of Allen and Smith [16].

Like Marvelon, Diane has been demonstrated to be effective in treatment of acne, both in comparison with baseline [17–19] and also with OCs containing levonorgestrel [17]. In a previous direct comparative study in France, Marvelon and Diane were equally effective in the treatment of mild to moderate acne [20]. This result is in line with the results of the present study.

Although it has been suggested that the anti-acne efficacy of Diane can be attributed to the anti-androgenic properties of cyproterone acetate, this is questioned by others: the contraceptive cyproterone acetate dose of 2 mg in Diane would be much too low to exert a clinically detectable effect. The absence of an important role of the cyproterone acetate dose in acne efficacy is supported by a study in which it was demonstrated that after 6 months of treatment there was no statistically significant difference in mean acne score between two preparations each containing 50 µg of ethinyl estradiol, but greatly different doses of cyproterone acetate (2 mg and 50 mg) [21]. Consequently, the anti-acne effect of Diane should probably be attributed mainly to the ethinyl estradiol component in the preparation [22]. In this respect, the results of the current study are remarkable, since the efficacy on acne was more or less similar with both study preparations, despite the lower daily

dose of ethinyl estradiol of 30 µg with Marvelon as compared to 50 µg with Diane.

The results of the present study on Oriental women are largely comparable to those obtained earlier on Caucasian women. Use of either Marvelon or Diane resulted in significant objective and subjective improvement of acne symptoms in the majority of Oriental women. In general, no marked between-group differences were detected.

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