CYPROTERONE ACETATE/ETHINYL ESTRADIOL IN THE TREATMENT OF ACNE. A COMPARATIVE DOSE-RESPONSE STUDY OF THE ESTROGEN COMPONENT

Pierre Fugère, M.D., FRCS (C)[1]
Robin K.L. Percival-Smith, M.D., B.Chir.[2]
Suzanne Lussier-Cacan, Ph.D.[3]
Jean Davignon, M.D., FRCP(C)[3]
Donald Farquhar, M.D., CCFP., FCFP.[2]

1 Hôpital Saint-Luc
Université de Montréal, Montréal, Québec
1058, rue Saint-Denis, Montréal, Québec, Canada

2 University of British Columbia
Vancouver, British Columbia

3 Institut de Recherches Cliniques de Montréal

ABSTRACT

The investigators compared 2 mg cyproterone acetate (CPA) in combination with either 0.035 mg or 0.050 mg ethinyl estradiol (EE_2) (Diane®-35 versus Diane®-50) in the treatment of acne. Both formulations of Diane® were highly effective in improving acne, even in women who had been refractory to other types of medication. Cycle control with both formulations was excellent and adverse effects were generally mild and confined to the first two cycles of treatment. Mean plasma lipid levels increased with both treatments, yet most individual values remained within normal limits after one year of therapy while the LDL-cholesterol/HDL-cholesterol ratio was stable throughout the study period. Plasma testosterone and DHEA-S levels paralleled the decline in the clinical severity of the acne. There was no loss of clinical effectiveness with Diane®-35 and it provided the advantage of a 30% decrease in the amount of estrogen.

INTRODUCTION

The concept of employing an anti-androgen, such as cyproterone acetate (CPA), with an estrogen such as ethinyl estradiol (EE_2), for hormonally dependent acne in women is based on sound therapeutic principles. In Europe, this combination (known as Diane®) has long been used for the treatment of signs of androgenization in women. Extensive multi-centre trials (1,2,3,4) have dramatically demonstrated its efficacy in acne patients, even among those who had been refractory to conventional treatment, including tetracycline and vitamin A acid (4).

The safety of Diane® as a contraceptive has also been demonstrated in thousands of women (1). Yet, in order to provide an even greater safety margin, ever decreasing levels of ethinyl estradiol have been employed in order to minimize the risk of cardiovascular complications and other estrogen-dependent side effects (5). In accordance

Submitted for publication March 7, 1990
Accepted for publication May 31, 1990

with this trend, a new lower dose formulation has been developed, which contains just 0.035 mg ethinyl estradiol (Diane®-35) instead of 0.050 mg (Diane®-50) found in the original formulation. The level of cyproterone acetate has remained at 2 mg.

From 1985 to 1988, a double-blind study of Diane®-35 versus Diane®-50 was undertaken at two Canadian centres in order to monitor the efficacy of the two strengths in women with androgen-dependent skin conditions. At the same time, the study afforded a valuable opportunity to evaluate the long-term (12 cycles) tolerance of both dose levels, their contraceptive effect, their effect on cycle control and plasma lipids and lipoproteins.

MATERIALS AND METHODS

Study Design and Drug Administration

The study followed a double-blind design for parallel groups. At each center, patients were randomly assigned one of the two treatments. Each cycle consisted of 21 days of Diane®-35 or Diane®-50 followed by a 7-day interval without medication. Treatment with both strengths began on Day 5 of the menstrual cycle. No allowance was made for a placebo group, since most patients used the medication as both a contraceptive and an anti-acne therapy. All previous systemic acne therapy was withdrawn within 6 weeks of starting the treatments. During the study, no concomitant anti-acne nor any other medication was permitted, except mild cleansing agents.

Patient Selection

Each patient enrolled in the study signed an approved informed consent form after the purpose and conditions of the trial had been carefully explained. Patients considered for inclusion were women in good general health, between the ages of 18 and 35 years, who presented with moderate to severe androgen-dependent acne vulgaris, defined as the presence of comedones, papules and macules on at least half of the face. The majority had been refractory to conventional topical or systemic therapy for acne. All patients underwent a complete physical and laboratory examination. None of the women were pregnant or contemplating a pregnancy and most required a contraceptive method.

Evaluations

Every three cycles, a gynecologist monitored body weight, blood pressure, cycle control and drug tolerance. The same dermatologist performed all the pretreatment and subsequent evaluations of acne severity. The specific response of the 3 types of acne lesions (comedones, papules, macules) as well as the overall severity of the acne condition was evaluated using the Cook's method (6).

Metabolic studies were undertaken in subgroups of patients at baseline and after 6 and 12 cycles of treatment. During the last week of active drug therapy, blood samples were taken following a 12-hour fast and plasma lipid and lipoprotein profiles [total cholesterol and VLDL-, LDL-, HDL2-, HDL3- cholesterol (C), triglycerides (TG), apolipoproteins (apo) A and B] were determined. The lipoproteins were separated under

standard conditions by a combination of ultracentrifugation and heparin-manganese precipitation of the apo B containing lipoproteins according to the Lipid Research Clinics Program (7). HDL2-C and HDL3-C levels were assayed according to the method of Gidez et al. (8). Plasma total and lipoprotein C and TG were measured enzymatically and VLDL- and LDL-apo B levels were determined by electroimmunoassay (9). Apo AI and AII were measured by immunoenzymometric assays (ELISA) (10). Results are available for 17 patients in the Diane®-35 group and 15 patients in the Diane®-50 group.

Statistics

The pretreatment demographic characteristics of the two treatment groups were tested by the Student t test to confirm that the groups were well matched. Results of the acne rating scales, cycle control data and laboratory data were submitted to an analysis of variance for a 2-factor experiment, the 2 factors being drugs and time. Tabulated data are presented as the mean ± standard deviation. The effect of individual treatment on plasma lipids and lipoproteins was analyzed by a one-way analysis of variance with repeated measures; the comparison of dosage effects was performed using a two-way analysis of variance with repeated measures on one factor. For all statistical analyses, the minimum level of significance was 5%.

RESULTS

A total of 40 patients treated with Diane®-35 and 33 patients treated with Diane®-50 were included in this evaluation. Of these, 56 had completed the full 12 cycles of treatment and the remainder at least 6 cycles. The comparative demographic data are provided in Table I. Apart from the difference in actual sample numbers, the two groups were well matched as to age, weight, height and smoking history.

Anti-Acne Effect

Table II provides the comparative ratings for Diane®-35 and Diane®-50 in the treatment of specific acne lesions (comedones, papules, macules) and overall severity over 12 cycles of treatment.

It shows that both formulations of Diane® provided significant improvement in all 3 types of acne lesions as well as for overall severity after 6 cycles as compared to the baseline ($p < 0.01$), with no significant differences between formulations. Further significant improvement was achieved in the assessment for macules at cycle 12 with both strengths of Diane® and in the assessment for papules at cycle 12 with Diane®-50.

At baseline, virtually all of the patients presented with acne lesions involving most of the face. At the conclusion of therapy, over two-thirds of the patients could be considered "cured", that is, they were either free of facial acne or exhibited just a few small, scattered lesions. The overall severity assessment mirrored this success, as significant improvement was evident at cycle 6 and 12 compared to the baseline ($p < 0.01$) (Table II). Between cycle 6 and 12, there was no further significant improvement.

TABLE I CHARACTERISTICS OF PATIENTS AT ENTRY

		DIANE®-35 N=40	DIANE®-50 N=33	t test
AGE (yrs)	Mean ± SD	22.7 ± 2.4	23.2 ± 4.1	0.6
	Range	17-30	17-35	
WEIGHT (kg)	Mean ± SD	58.5 ± 11.7	57.3 ± 6.6	0.5
	Range	42.5-85.3	42.3-68.6	
HEIGHT (cm)	Mean ± SD	162.6 ± 9.3	160.7 ± 6.6	0.9
	Range	151-178	148-175	
SMOKERS	Yes	7	6	
	No	33	27	

Considering that most patients had been refractory to other anti-acne medication, there were remarkably few non-responders in this study. Some 43 patients (59%) from both treatment groups were rated with severe facial acne prior to Diane® treatments. After 12 cycles, the condition remained severe in only 5 patients (7%).

Cycle Control

Throughout the study, the average length of cycle (28 days) and average duration of menstruation (5 days) remained remarkably constant with both formulations. In fact, the drugs frequently normalized the menstrual period in individuals whose pretreatment periods were abnormally long. Menstrual flow tended to decrease somewhat with time, which actually represented a normalization in some 12 patients who had experienced excessive blood flow prior to treatment. There were no pregnancies. Cycle deviations were rare. Amenorrhea did not occur at all in the Diane®-50 group and occurred only sporadically in the Diane®-35 group (1.3% of the 480 treated cycles) (Table III). Spotting appeared occasionally with both formulations but never in more than 2 consecutive cycles with the same patient. Spotting was reported at a rate of 3.1% with Diane®-35 and 2.5% with Diane®-50 (Table III). Breakthrough bleeding occurred in 2 cycles with Diane®-35 (0.4%) and in 4 cycles with Diane®-50 (1%).

Dysmenorrhea was a common pretreatment finding in both treatment groups (73% and 76% in the Diane®-35 and Diane®-50 groups, respectively). With continued treatment the incidence showed a decrease with an overall improvement after 12 cycles of treatment in 83% of the Diane®-35 patients and in 64% of the Diane®-50 patients.

Lipid and Lipoprotein Profile

A lipid profile was generated for both groups of patients at baseline and at cycle 6 and 12 (Table IV). With both formulations, there was a significant increase in total cholesterol and triglycerides as compared to pretreatment values. The percent overall increase in total

TABLE II EFFECT OF DIANE®-35 AND DIANE®-50 ON COMEDONES, PAPULES, MACULES AND OVERALL SEVERITY OVER 12 CYCLES OF TREATMENT

	Mean Scores@							
	DIANE®-35			DIANE®-50				
	N=40	N=39	N=37	N=33	N=32	N=25	p	p
CYCLE	0	6	12	0	6	12	(between drugs)	(with time)
COMEDONES	3.5	1.7*	1.2*	3.3	1.4*	1.0*	NS	<0.01
PAPULES	4.2	1.8*	1.3*	4.1	1.8*	1.1*+	NS	<0.01
MACULES	3.9	1.9*	1.1*+	3.6	1.8*	1.0*+	NS	<0.01
OVERALL SEVERITY	4.8	2.0*	1.4*	4.3	1.8*	1.2*	NS	<0.01

*Significant improvement vs. baseline + Significant improvement vs. cycle 6

@Scoring: Lesions:
0 - A few lesions are permitted; they are small and it is necessary to search for them.
1 - There are only a few lesions, but they are easily recognizable.
2 - Greater than grade 1; easily recognizable; most of the face is clear.
3/4 - Progressively more lesions; greater areas of the face are involved.
5 - About half of the face is involved
6/7 - Progressively more lesions; more than half the face is involved at grade 6.
8 - Most of the face is involved.
9 - The entire face is generally covered with lesions.

Overall Severity:
0 - Need not be perfect ; perhaps 3 small comedones and/or small papules are allowed, if they are scattered.
2- Very few pustules or perhaps 3 dozen papules and/or comedones; no big or prominent lesions; lesions are hardly visible from 2.5 m away.
4 - Between 2 and 6, there are red lesions and inflammation to a significant degree; worthy of treatment.
6 - Loaded with comedones; no inflammation; or inflammatory lesions; must have numerous pustules; lesions are easily recognized at 2.5 m; some pustules may be quite large, 1 to 2 cm.
8 - Conglobate, sinus or cystic type acne; or a highly inflammatory acne covering most of the face; yellow pustules extend to neck and chin

TABLE III EFFECT OF DIANE®-35 AND DIANE®-50 ON CYCLE CONTROL

CYCLE	1	2	3	4	5	6	7	8	9	10	11	12	Events/ no. of cycles	%	p
AMENORRHEA															
Diane®-35	0	0	1	1	1	1	1	1	0	0	0	0	6/480	1.3	NS
Diane®-50	0	0	0	0	0	0	0	0	0	0	0	0	0/396	0	
SPOTTING															
Diane-®-35	2	3	0	1	2	3	2	1	0	0	1	0	15/480	3.1	NS
Diane®-50	3	1	1	1	0	0	1	1	0	1	1	0	10/396	2.5	
BREAKTHROUGH BLEEDING															
Diane®-35	0	0	0	2	0	0	0	0	0	0	0	0	2/480	0.4	NS
Diane®-50	1	0	0	0	0	0	0	0	0	1	1	1	4/396	1.0	

Diane®-35 N=40 Diane®-50 N=33

cholesterol was higher (20%) in the Diane®-35 group that in the Diane®-50 group (13%), this difference being primarily due to LDL-C (19% and 8%, respectively).

After 6 cycles, HDL2-C was significantly higher only in the Diane®-35 group, while HDL3-C showed a similar progressive increase in both treatment groups. LDL-C and HDL-C levels both increased, therefore the LDL-C/HDL-C ratio did not change significantly in either group.

The reverse was true with triglycerides, which showed a greater increase ($p<0.05$) in the Diane®-50 group (81%) than in the Diane®-35 group (62%) at cycle 12. The higher value in the Diane®-50 group was related to a higher VLDL-TG, the TG carried by the TG-poor lipoproteins (LDL+HDL) increasing significantly and equally in both groups. The TG enrichment of this fraction relative to its C content caused a significant reduction ($p<0.01$) in the C/TG ratio at both cycle 6 and 12.

The data shown in Table IV suggest that increases in lipids and lipoproteins may have peaked around the 6th cycle, as most showed no further increase and some values, particularly those of triglycerides, decreased in the Diane®-50 group. LDL-C/HDL-C ratios still remained unchanged. LDL-apo B levels increased significantly but proportionally with LDL-C and consequently, the LDL-C/LDL-apo B ratio was not significantly affected (data not shown). Apo AI and Apo AII levels were significantly higher after 6 and 12 cycles of treatment with both formulations. There was no significant difference between groups.

Endocrinological Evaluations

Prior to treatment, plasma levels of testosterone were, respectively, 65 ± 35 mg/dl and 56 ± 30 mg/dl for the Diane®-35 and Diane®-50 groups. By the end of the 6th cycle of treatment, the plasma testosterone levels fell to 22 ± 10 mg/dl and 15 ± 9 mg/dl for the respective groups. This reduction, which was significant at $p<0.01$, was maintained throughout the following 6 cycles. Similarly, the DHEA-S plasma values were elevated at baseline (266 ± 91 mg/dl and 253 ± 128 mg/dl) in the Diane®-35 and Diane®-50 groups, respectively. Levels in both groups fell to 170 ± 69 mg/dl and 144 ± 77 mg/dl, respectively, after 6 cycles of treatment and remained low during the following 6 cycles ($p<0.01$).

Safety and Tolerance

With both formulations, mean systolic and diastolic blood pressures remained stable throughout the study. Body weight tended to increase slightly in both groups, but there were no significant changes and most patients remained within ± 2 kg of their starting weight.

Nausea, headache and breast tension were the most common symptoms, but these tended to disappear after the second cycle. The tolerance picture with both formulations of Diane® was similar in terms of the incidence and severity of adverse effects. There were no serious endocrine, cardiovascular or hepatic complications, nor were there any emerging signs of chloasma, edema, thrombophlebitis or hepatopathy.

TABLE IV EFFECT OF DIANE®-35 AND DIANE®-50 ON LIPID AND LIPOPROTEIN PROFILE OVER 12 CYCLES OF TREATMENT

Variable	Mean ± standard deviation (SD) in mg/dl				
Cycle	0	6	p	12	p
Total C					
D-35	155(27)	186(41)	<0.001	185(30)	<0.001
D-50	164(22)	181(20)	<0.002	186(19)	<0.001
Total TG					
D-35	66(35)	96(42)	<0.01	96(16)	<0.005
D-50	79(44)	133(65)*	<0.001	123(52)	<0.001
VLDL-C					
D-35	14(6)	20(10)	NS	24(7)	<0.001
D-50	18(9)	25(11)	<0.01	27(8)	<0.005
VLDL-TG					
D-35	48(30)	58(30)	NS	61(13)	NS
D-50	58(34)	92(52)*	<0.001	86(39)	<0.01
LDL-C					
D-35	90(25)	107(37)	<0.01	104(30)	<0.05
D-50	95(20)	101(22)	NS	99(22)	NS
HDL-C					
D-35	50(13)	60(15)*	<0.001	57(14)	<0.01
D-50	52(12)	55(10)	<0.02	60(13)	<0.001
HDL2-C					
D-35	21(10)	25(10)*	<0.01	22(10)	NS
D-50	23(10)	22(9)	NS	24(9)	NS
HDL3-C					
D-35	29(5)	34(7)	<0.001	35(5)	<0.001
D-50	28(4)	33(4)	<0.001	36(6)	<0.001
LDL-+HDL-TG					
D-35	19(7)	38(16)	<0.001	37(10)	<0.001
D-50	21(15)	41(16)	<0.001	37(15)	<0.001
VLDL-apo B					
D-35	9(7)	11(7)	NS	13(5)	NS
D-50	10(6)	18(5)	<0.02	15(6)	NS
LDL-apo B					
D-35	80(14)	96(32)	<0.01	92(24)	<0.02
D-50	81(17)	87(17)	<0.06	92(19)	<0.01
Apo AI					
D-35	98(24)	122(28)	NS	146(29)	<0.001
D-50	91(22)	124(34)	NS	159(41)	<0.001
Apo AII					
D-35	31(7)	43(9)	NS	44(9)	<0.001
D-50	31(4)	40(9)	NS	41(10)	<0.001
LDL-C/HDL-C					
D-35	1.94(0.74)	1.89(0.70)	NS	1.93(0.64)	NS
D-50	1.97(0.73)	1.92(0.67)	NS	1.77(0.64)	NS

*Significant difference between treatment groups ($p<0.05$)

DISCUSSION

The objective of this investigation was to determine whether Diane®-35, with its lower concentration of estrogen, can be used as effectively as and possibly more safely than Diane®-50 in the treatment of androgen-dependent acne. Clinically, the lower dose formulation was just as effective and appeared to provide certain advantages. The data revealed that both formulations provided significant and sustained improvement in acne over 12 cycles of treatment. All categories of acne lesions were found to respond and no significant between-treatment differences were seen over the long-term treatments. In both treatment groups, cycle control was excellent and there were no pregnancies. Adverse effects were generally mild and usually subsided after the second cycle; occasionally, breast tension persisted through the 6th cycle.

Like other investigators (11), we found that mean lipid levels increased over the initial 6 cycles of treatment. The relative rise in total cholesterol and LDL-C was slightly greater with Diane®-35 , while the increase in TG was less than with Diane®-50. The increase in HDL-C was due primarily to HDL3-C in both groups. After 12 cycles, the only significant differences between treatment groups were the values for total- and VLDL-triglycerides, both of which being higher with Diane®-50, and LDL-C which was higher with Diane®-35. After 6 cycles, lipid and lipoprotein levels tended to plateau or decline. Triglycerides showed the greatest decrease. Despite these observed changes, the average values remained within normal limits after 12 cycles of therapy and the LDL-C/HDL-C ratios never fluctuated throughout the 12 cycles of the study. In the Diane®-50 group, there were certain individuals, however, who maintained abnormally high TG levels. Therefore, it seems that, as with low-dose oral contraceptives (12), adaptation to the long-term use of Diane® occurs in most cases without significant adverse changes in the lipoprotein profile and without any decrease in HDL-C.

Analyses of plasma testosterone and DHEA-S levels demonstrated the potency of the cyproterone acetate component of the drug. The parallel decline in testosterone with the remission of severe acne supports the use of hormonal therapy in androgen-dependent acne in women.

In conclusion, the behaviours of the two strengths of Diane® have been shown to be nearly identical. There was no loss of clinical effectiveness with the lower dose formulation; on the contrary, Diane®-35 may be superior in terms of the time of onset and the early magnitude of effect. Acne demands long-term therapy and for this reason, the low-dose formulation offers an advantage, as it represents a 30% decrease in the total amount of estrogen administered to women.

REFERENCES

1. Schering AG. Data on file, Berlin/Bergkamen. West Germany.

2. Gaspard UJ, Romus MA, Soyeur-Broux M, Chantraine R, Duvivier J. Clinical, endocrinological and metabolic evaluation of women treated for acne by a combination of cyproterone acetate and ethinyl estradiol (Diane) In: Vokaer R, Fanta D, eds. Combined antiandrogen-estrogen therapy in dermatology. Amsterdam: Excerpta Medica, 1981:75-94.

3. Keller PJ. Clinical experience with antiandrogenic oral contraceptives. In: Vokaer F, Fanta D, eds. Combined antiandrogen-estrogen therapy in dermatology. Amsterdam: Excerpta Medica, 1981:95-100.

4. Khodjasteh Z, Copinschi G, Lejeune-Lenain C, Franckson JRM, Robyn C. Hormonal profile on acne before and during 6 months' Diane® administration. In: Vokaer R, Fanta D, eds. Combined antiandrogen-estrogen therapy in dermatology. Amsterdam, Excerpta Medica, 1981:101-107

5. Fotherby F. Oral contraceptives, lipids and cardiovascular disease. Contraception 1985:32:367-394.

6. Cook H, Centner RL, Michaels SE. An acne grading method using photographic standards. Arch Dermatol 1979:115:571-575.

7. Lipid Research Clinics Program: Manual of Laboratory Operations. Lipid and lipoprotein analysis. Dept of Health, Education and Welfare - NIH Publication. No. 76-62B. U.S. Government Printing Office, Washington, D.C. Vol 1 , 1974: 1-81.

8. Gidez LI, Miller J, Burstein M, Slagle S, Eder HA. Separation and quantitation of subclasses of human plasma high density lipoproteins by a simple precipitation procedure. J Lipid Res 1982:23:1206-1223

9. Lussier-Cacan S, Bouthillier D, Davignon J. Apo E allele frequency in primary endogenous hypertriglyceridemia (Type IV) with and without hyperapobetalipoproteinemia. Arteriosclerosis 1985:5:639-643.

10. Fruchart JC, Fiévet C, Puchois P. Apo-lipoproteins. Metabolites III: lipids, amino acids and related compounds. In: Bergmeyer HU, ed. Methods of enzymatic analysis. N.Y.: VCH Publications, 1985:126-138

11. Thulliez M. Diane: Le point de vue d'un dermatologue belge. In: Vokaer F, Fanta D. eds. Combined antiandrogen-estrogen therapy in dermatology. Amsterdam: Excerpta Medica, 1981:71-73

12. Notelovitz M, Feldman EB, Gillespy M, Gudat J. Lipid and lipoprotein changes in women taking low-dose triphasic oral contraceptives: A controlled, comparative, 12-month clinical trial. Am J Obstet Gynecol 1989:160: 1269-1280.