

Clinical Efficacy of Low Dose Flutamide plus Diane-35 in the Treatment of Idiopathic Hirsutism and Polycystic Ovary Syndrome

Ocena skuteczności klinicznej niskodawkowego flutamidu i Diane-35 w leczeniu idiopatycznego hirsutyizmu i zespołu policystycznych jajników

Abdullah Boztosun¹, Gökhan Açmaz², Ahmet Ozturk³, İptisam İpek Müderris⁴

¹ Department of Obstetrics and Gynecology, Cumhuriyet University School of Medicine, Sivas, Turkey

² Department of Obstetrics and Gynecology, Kayseri Training and Education Hospital of Medicine, Kayseri, Turkey

³ Department of Statistics, Erciyes University School of Medicine, Kayseri, Turkey

⁴ Department of Obstetrics and Gynecology, Erciyes University School of Medicine, Kayseri, Turkey

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The Diane-35® (Bayer [South East Asia] Pte Ltd, Singapore)

125mg flutamide (Eulexin, Schering)

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Abstract

Objective: Idiopathic hirsutism (IH) or polycystic ovary syndrome (PCOS) are the most common causes of hirsutism which affects 5–10 % of all women. The aim of this study was to evaluate the efficacy of flutamide plus Diane 35 in the treatment of idiopathic hirsutism and polycystic ovary syndrome.

Materials and Methods: 26 polycystic ovary syndrome and 24 idiopathic hirsutism patients were evaluated. Fifty patients were divided into two groups according to their diagnosis: idiopathic hirsutism or polycystic ovary syndrome. All patients received 125mg Flutamide once a day and Diane 35 tablets for 21 days of each month, for 12 months. We measured hirsutism scores and hormonal levels of all patients. Evaluations were done before treatment, in the 6th and 12th months of therapy.

Results: There were no significant differences in Ferriman-Gallwey scores at the beginning and at the end of the therapy between the IH and PCOS groups. The decreases in Ferriman-Gallwey scores were significant in both groups in the 6th and 12th month of therapy. Combined treatment significantly decreased total and free testosterone, DHEAS and significantly increased SHBG levels in both groups and additionally decreased levels of LH, androstenedione and LH/FSH ratio in the polycystic ovary syndrome group.

Conclusion: Combined treatment was effective and safe in the treatment of hirsutism. Combined regimens have additional effects on the treatment of hirsutism.

Key words: **Hirsutism / Flutamid / Diane-35a /**

Corresponding address:

Gökhan Açmaz

Department of Obstetrics and Gynecology, Kayseri Training and Education Hospital of Medicine, Kayseri, Turkey

tel: +90 535 654 07 03

e-mail: gokhanacmaz@mynet.com

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Streszczenie

Cel: Idiopatyczny hirsutyzm (IH) oraz zespół policystycznych jajników (PCOS) są najczęstszymi przyczynami hirsutyizmu, który dotyka 5-10% wszystkich kobiet. Celem pracy była ocena skuteczności flutamidu i Diane 35 w leczeniu idiopatycznego hirsutyizmu i zespołu policystycznych jajników.

Materiał i metoda: Zbadano 26 kobiet z zespołem PCO i 24 z idiopatycznym hirsutyizmem. Stanowiły one dwie grupy badane. Wszystkie pacjentki otrzymały 125mg flutamidu raz dziennie i Diane-35 przez 21 dni. Leczenie trwało 12 miesięcy. Zmierzono nasilenie hirsutyizmu i poziom hormonów u badanych pacjentek przed leczeniem oraz po 6 i 12 miesiącach terapii.

Wyniki: Nie znaleziono istotnych różnic w skali Ferrimana-Gallwaya na początku i na końcu leczenia pomiędzy grupą z IH a grupą PCOS. Zmniejszenie nasilenia hirsutyizmu wg skali Ferrimana-Gallwaya było istotne w obu grupach w 6 i 12 miesiącu terapii. Skojarzone leczenie istotnie zmniejszało całkowity i wolny testosteron, DHEAS i istotnie zwiększało poziom SHBG w obu grupach badanych. Dodatkowo zmniejszała poziom LH, androstendionu i stosunek LH/FSH w grupie z policystycznymi jajnikami.

Wnioski: Skojarzone leczenie hirsutyizmu jest skuteczne i bezpieczne. Skojarzone dawki mają sumarycznie większy wpływ na leczenie hirsutyizmu.

Słowa kluczowe: **hirsutyizm / flutamid / Diane-35 /**

Introduction

Hirsutism is a disorder which becomes present with a male type hair and male type distribution that may be the consequence of either androgen excess or increased sensitivity of hair follicles to normal levels of androgens.¹ Idiopathic hirsutism (IH) or polycystic ovary syndrome (PCOS) are the most common causes of hirsutism which affects 5–10% of all women. Both of them are very distressing conditions for women.² Mechanical hair removal is an effective way of treatment among many hirsute women. However, pharmacological approach is usually required in patients with moderate to severe hirsutism to suppress androgen production and/or action.

Flutamide is an effective drug for women with IH or PCOS. This drug is a pure peripheral androgen antagonist with no progestogenic or antigonadotropic action and reduces the synthesis of androgens or increases their metabolism.³ Some of the researchers described a relationship between amenorrhea and flutamide used during the treatment of hirsutism.⁴ However, flutamide has non-steroidal shape therefore it is reasonable not to expect menstrual irregularity.⁵

Cyproterone acetate (CPA) is a 17-hydroxyprogesterone acetate derivative that competes with dihydrotestosterone (DHT) for the androgen receptor and reduces LH levels which decrease testosterone and androstenedione levels.⁵ CPA has antiandrogenic and antigonadotropic activity and is ideal for hyperandrogenic hirsutism.⁶ Combination with CPA/ethinyloestradiol (EE) can help ensure an adequate estrogen input and allow regular bleeding.⁷ Combined oral contraceptives (COCs) are an accepted first step traditional treatment modality of hirsutism and they effectively suppress ovarian androgen production.⁸ Their progestational activity reduces LH secretion and lowers the release of LH-mediated ovarian androgen. Estrogenic component of COCs increases sex hormone-binding globulin (SHBG) which decreases the amount of free testosterone (FT).⁹

The Diane-35® (Bayer [South East Asia] Pte Ltd, Singapore) is a combination of CPA and EE. The objective of the present study was to evaluate the efficacy of 125mg flutamide (Eulexin, Schering) plus Diane-35 in the treatment of hirsutism.

Material and methods

Fifty hirsute female patients of our reproductive endocrinology clinic were enrolled in the study. Hirsutism evaluation was measured using the modified Ferriman–Gallway (mFG) scoring method described by Hatch et al.¹⁰ All scores were measured by the same specialist and after the examination the patients were divided into two groups, according to their diagnosis, IH or PCOS. The study was approved by the Ethical Committee of Erciyes University. Written informed consent was obtained from all the participants at the ages between 16 and 43. None of the patients had history of hypertension, thromboembolic disease, diabetes mellitus, cardiovascular events, or received treatment with COCs, antiandrogens or insulin sensitizers for 6 months prior to the study.

Of the 50 patients, 26 (52%) were diagnosed with PCOS and 24 (48%) with IH. We proposed that a diagnosis of IH should only be made in hirsute patients who have normal androgen levels and regular ovulatory menstrual cycles.¹¹⁻¹² The diagnosis of PCOS was made according to the Rotterdam PCOS Consensus.¹³ Ultrasonographic diagnosis of polycystic ovaries was based on the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume >10 ml on pelvic or vaginal ultrasound examination.¹⁴ Oligo/amenorrhea were defined as the absence of menstruation for 35 days or more.¹⁵

All patients received 125mg flutamide once a day and Diane 35, for 21 days of each month in the course of 12 months. The therapy was started on the first day of the menstrual cycle. Blood samples were taken during the mid-follicular phase of the menstrual cycle. Hormonal analyses included FSH, LH, SHBG, 17alpha-hydroxyprogesterone (17-OHP), E2, androstenedione, total testosterone (TT), FT, PRL and DHEAS.

Clinical side effects were assessed monthly by examining a range of biochemical parameters. Patient complaints, i.e. potential side effects, were recorded each month. Hormonal tests and hirsutism scores (HS) were evaluated in 6th and 12th month of the therapy. After centrifugation, blood serum was stored at –20°C until assayed. Serum TT, FT, androstenedione, DHEAS, FSH, LH, E2 and 17-OHP were measured by radioimmunoassay

using commercial kits (DPC, Los Angeles, Ca, USA). SHBG was measured by immunoradiometric assay (Orion Diagnostica, Espo, Finland). The intra- and inter-assay precision coefficients of the variation were 3.2% and 4.4% for FSH, 6.8% and 7.9% for LH, 5.2% and 5.5% for E2, 10% and 10.4% for testosterone, 4.3% and 5.5% for FT, 8.3% and 9.2% for androstenedione, 39% and 7.0% for DHEAS, 5.6% and 4.5% for 17-OHP, and 4.0% and 5.5% for SHBG respectively. All results are given as means \pm sd.

Statistics

All continuous variables were reported as mean \pm standard deviation. Changes in the serum hormone levels among baseline and 6th and 12th month of therapy with PCOS and IH were analyzed by two way analysis of variance for repeated measures. The adjustment for multiple comparisons was performed with the Bonferroni correction. Independent proportions between groups were compared with the chi-square test. Differences between the groups were evaluated using an unpaired t test. A p value of <0.05 was regarded as statistically significant. Analysis was performed with the Statistical Package for the Social Sciences version 15.0 (SPSS Inc, Chicago, IL, USA).

Results

The baseline characteristics of the two treatment groups were similar. The mean age of the PCOS and IH groups was 25.23 ± 7.27 and 25.17 ± 6.95 years, respectively ($p>0.05$). Normal values for the FG score are less than 8, so the degree of hirsutism in both groups was considerable. The mean value of mFG score was 21.85 ± 5.96 in the PCOS group and 19.88 ± 4.85 in the IH group ($p>0.05$). The mean value of BMI in the IH group was generally normal (mean BMI, 23.67). Although the PCOS group was slightly overweight (mean BMI, 25.50), there was no statistically significant difference between the two groups ($p>0.05$). Oligo/amenorrhea was detected in 21 of 26 patients in the PCOS group and, naturally, we did not detect menstrual irregularity in the IH group. At the end of the treatment no menstrual irregularity was detected in either group. Overall, both drugs were found to be well-tolerated. No serious side effects were detected in the patients.

Table 2 shows the hormone levels and HS during therapy in the PCOS and IH groups. The HS before treatment, in the 6th and 12th month of the treatment were similar in both groups. In the group IH the percent reduction in HS was $42.8\pm 12.5\%$ and $64.3\pm 11.4\%$ in the 6th and 12th month of the therapy, respectively. In the PCOS group it was $37.6\pm 17\%$ and $64.8\pm 13.8\%$ in the 6th and 12th month of the therapy. The percent reduction in HS was not different between the IH and PCOS groups ($p>0.05$).

Basal hormonal measurement shows that LH, TT, FT, androstenedione and LH/FSH levels were significantly elevated in the PCOS group ($P<0.05$) There were no significant differences in all hormone levels and LH/FSH level between the 6th and 12th month of therapy in both groups; only SHBG levels showed statistically significant increase in the PCOS group.

Flutamide plus CPA/EE treatment significantly decreased TT, FT, DHEAS, androstenedione, LH and LH/FSH ratio and significantly increased SHBG levels after the first 6 months of treatment in the PCOS group. We detected significant decrease of TT, FT, DHEAS, FSH, OHP and increased levels of SHBG but there were no statistically significant results for LH and LH/FSH

Table 1. Baseline characteristics of groups.

Variable	Group (IH)	Group (PCOS)	p
BMI	23.67 \pm 3.11	25.50 \pm 4.60	0.108
Age	25.17 \pm 6.95	25.23 \pm 7.27	0.980

ratio in the IH group. Comparison of basal and end of therapy showed statistically significant decrease of TT, FT and DHEAS and increased SHBG levels in both groups. Additionally, decreased levels of LH, androstenedione and LH/FSH ratio were found in the PCOS group. All binary comparisons for HS and hormonal levels in the time periods (6th and 12th month) revealed no statistically significant differences between the IH and PCOS groups.

Discussion

Hirsutism is a common clinical condition in women and is characterized by excessive growth of terminal hair in the androgen sensitive skin regions. This study has shown that flutamide plus CPA/EE have an additional, beneficial effect on women with hirsutism.

Some authors suggest that flutamide reduces androgen synthesis by restoring ovulation, although a direct block of the steroidogenic enzymes of androgen biosynthesis in ovarian thecal cells cannot be excluded.¹⁶ Flutamide treatment has been reported not to affect gonadotropins, E2, and P levels and, therefore, does not alter the mechanism of ovulation.⁶ Because of peripheral antiandrogenic effect, flutamide has a potential risk of feminization on a male fetus which requires the use of a contraceptive method during flutamide treatment of hirsutism. Thus, a combined treatment may be a good choice in women with hirsutism.¹⁷

Flutamide treatment can be complicated by skin dryness, gastrointestinal discomfort, breast tenderness and hepatotoxicity. The reported incidence of these side effects increases with higher doses. When long-term treatment is introduced, it is worth noting that the use of a low dose reduces both the cost of the treatment and the possible side effects.¹⁸ In terms of dosage the efficacy of low-dose flutamide therapy on hirsutism has been observed to be similar to that of higher daily doses.¹⁹ In our study low-dose flutamide was administered at a low-dose.

COCs have been established to reduce circulating androgen levels through the suppression of circulating LH and the stimulation of SHBG levels.²⁰ The former mechanism is common to all COCs and reflects the progestin mediated suppression of gonadotropin release and subsequent reduction of the ovarian androgen synthesis. CPA/EE has previously been reported to significantly decrease TT, FT, androstenedione, DHEAS, and DHT levels and to increase SHBG levels in hirsute women.²¹

Calaf et al., claimed that flutamide plus COCs reduced HS by 52.7% after 12 months of daily treatment. Our reduction is even higher than that obtained by Calaf et al., what may be linked with the fact that they used triphasic OC in their study. Additionally, all subjects in their study were premenopausal and Calaf et al., did not administer CPA to the patients. They

Table II. Hormonal levels and hirsutism scores before and during treatment in IH (n = 24) and PCOS (n = 26).

	Level at indicated month of treatment			F	p [*]	p [†]	p [‡]
	Baseline	6 months	12 months				
HS							
IH	19.88 ± 4.85 ^a	11.54 ± 4.17 ^b	7.00 ± 2.59 ^c	377.65	<0.001	0.319	0.162
PCOS	21.85 ± 5.96 ^a	13.81 ± 5.61 ^b	7.85 ± 3.86 ^c				
TSH							
IH	1.56 ± 0.84 ^a	1.32 ± 0.79 ^{ab}	1.28 ± 0.79 ^b	3.38	0.038	0.738	0.192
PCOS	1.75 ± 0.84 ^{ab}	1.58 ± 0.63 ^{ab}	1.61 ± 0.78 ^{ab}				
PRL							
IH	12.86 ± 7.25	10.90 ± 5.32	10.96 ± 3.97	2.64	0.076	0.850	0.298
COS	13.89 ± 7.67	12.85 ± 4.69	12.24 ± 5.27				
FSH							
IH	7.00 ± 2.58 ^a	6.00 ± 1.78 ^b	5.74 ± 2.03 ^b	5.69	0.005	0.354	0.513
PCOS	6.29 ± 2.32 ^{ab}	5.61 ± 1.93 ^{ab}	5.86 ± 1.84 ^{ab}				
LH							
IH	5.33 ± 2.01 ^a	4.89 ± 1.34 ^a	4.43 ± 1.93 ^a	28.52	<0.001	<0.001	<0.001
PCOS	9.18 ± 3.93 ^b	5.09 ± 1.72 ^a	4.70 ± 1.30 ^a				
E2							
IH	57.64 ± 34.50	51.51 ± 26.90	47.28 ± 26.56	2.83	0.064	0.657	0.514
PCOS	53.53 ± 36.62	43.31 ± 21.26	46.58 ± 23.09				
OHP							
IH	1.20 ± 1.16 ^a	0.91 ± 0.76 ^b	0.96 ± 0.88 ^{ab}	3.18	0.046	0.630	0.193
PCOS	0.87 ± 0.65 ^{ab}	0.75 ± 0.36 ^{ab}	0.72 ± 0.43 ^{ab}				
SHB							
IH	64.50 ± 36.84 ^a	88.23 ± 47.25 ^b	99.06 ± 55.48 ^{bc}	30.10	<0.001	0.601	0.850
PCOS	64.17 ± 32.68 ^a	80.84 ± 39.92 ^b	100.37 ± 47.97 ^c				
DHE							
IH	2386.53 ± 1075.25 ^a	2008.62 ± 971.89 ^b	1914.33 ± 782.60 ^b	25.36	<0.001	0.596	0.870
PCOS	2430.77 ± 944.09 ^a	1972.77 ± 727.01 ^b	1792.81 ± 684.69 ^b				
AND							
IH	2.80 ± 1.67 ^a	2.55 ± 1.14 ^a	2.43 ± 1.20 ^a	8.84	<0.001	0.148	0.173
PCOS	3.61 ± 1.69 ^b	2.76 ± 1.12 ^a	2.83 ± 1.26 ^a				
TT							
IH	67.57 ± 25.10 ^a	52.94 ± 23.61 ^b	51.08 ± 23.79 ^b	35.49	<0.001	0.005	0.020
PCOS	96.17 ± 38.05 ^c	64.49 ± 20.29 ^b	56.85 ± 25.02 ^b				
ST							
IH	2.04 ± 0.93 ^a	1.45 ± 0.66 ^b	1.32 ± 0.57 ^b	42.65	<0.001	0.070	0.011
PCOS	2.79 ± 1.06 ^c	1.78 ± 0.64 ^b	1.59 ± 0.55 ^b				
LHFSH							
IH	0.78 ± 0.32 ^a	0.97 ± 0.80 ^a	1.09 ± 1.10 ^a	1.48	0.233	<0.001	0.132
PCOS	1.55 ± 0.56 ^b	1.02 ± 0.51 ^a	0.88 ± 0.37 ^a				

IH, idiopathic hirsutism; PCOS, polycystic ovary syndrome; HS, hirsutism score; TSH, thyroid stimulating hormone; PRL, prolactin; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estradiol; OHP, 17 α -hydroxyprogesterone; SHB, sex hormone-binding globulin; DHE, dehydroepiandrosterone sulfate; AND, androstenedione; TT, total testosterone; FT, free testosterone; LHFSH, ...; data expressed as mean±standard error; analysis was carried out by two-way analysis of variance for repeated measures, groups with different superscript letters were found to have statistically significant differences; *test of within-subjects effects; †interaction between both regimens; ‡test of between-subjects effects.

measured a standard hormonal profile, including serum levels of PRL, E2, FT, DHEAS, androstenedione, 17-OHP, SHBG, TT, LH, and FSH, and found that flutamide plus COCs increased SHBG and decreased all of the hormones, except for prolactin.²²

CPA is an anti-androgen with progestational activity, currently used for treating hirsutism. CPA inhibits gonadotropin secretion and competes with DHT for binding to the androgen receptor. Diane plus flutamide therapy enabled us to decrease androgen levels of both glandular and peripheral origins, and interfere with the interaction of dihydrotestosterone and its intracellular receptor. We believe that the combination of the

two drugs may occupy more receptors than the one drug alone occupies.

In the light of the results of our study it seems safe to conclude that flutamide plus Diane35 regimen has additional, beneficial effects on the treatment of hirsutism and the contraceptive treatment helps to regulate menstruation, especially of PCOS patients. Menstrual regulation improves patient satisfaction and helps them take their medicines regularly. However, flutamide has a potential risk of feminization on a male fetus so combining the therapy with a contraceptive treatment may be a good choice in women with hirsutism.

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POLSKIE TOWARZYSTWO KOLPOSKOPII I PATOFIZJOLOGII SZYJKI MACICY,
KATEDRA GINEKOLOGII I POŁOŻNICTWA UJCM,

ZGŁOSZENIA: 124248560, 124248584,
e-mail: **onkologia@cm-uj.krakow.pl**

lub poprzez stronę internetową:

www.kolposkopia.info

Opłaty:

Kongres:	600 zł
Kurs:	600 zł
Egzamin:	300 zł
Cena kongresu i kursu:	800 zł + 300 zł (egzamin)