Müderris & Öner (2009) - Hirsutizm Tedavisinde Flutamid ve Bikalutamid Kullanımı [Flutamide and Bicalutamide Treatment in Hirsutism]

Citation

- Müderris, İ. İ., & Öner, G. (2009). Hirsutizm Tedavisinde Flutamid ve Bikalutamid Kullanımı. [Flutamide and Bicalutamide Treatment in Hirsutism.] *Türkiye Klinikleri Endokrinoloji-Özel Dergisi* [*Türkiye Klinikleri Endocrinology-Special Topics*], *2*(2), 110–112. [ISSN:1308-0954] [URL] [PDF]

English Translated

Flutamide and Bicalutamide Treatment in Hirsutism

Dr. İptisam İpek MÜDERRİS,[a] Dr. Gökalp ÖNER[a]

[a] Department of Gynecology and Obstetrics, Erciyes University Faculty of Medicine, Kayseri

Correspondence:
Dr. İptisam İpek MÜDERRİS
Erciyes University Medical Faculty, Obstetrics and Gynecology, Kayseri, TURKEY
imuderris@erciyes.edu.tr

ABSTRACT Hirsutism is a distressing and relatively common endocrine problem in women which is a common clinical problem in women of reproductive age, is characterized by excessive growth of terminal hair in the androgen-sensitive skin regions. Anti-androgen treatment often needs to be continued for a long time. So, safe, inexpensive, and effective anti-androgen drugs are needed. Flutamide and bicalutamide have been used successfully in the treatment of hirsutism. However, flutamide and bicalutamide may cause important side-effects which may result in cessation of the drug. A very long treatment period is always required to improve hirsutism and prevent or delay its relapse; the use, as much as possible, of low doses of antiandrogens may be a suitable choice in an attempt to prevent the incidence of side-effects and complications and to maintain treatment. The present review confirms the effectiveness of two antiandrogens, flutamide and bicalutamide, in the treatment of hirsutism, even if given in very low doses; however, some differences do exist.

Key Words: Flutamide, bicalutamide, hirsutism, treatment

Turkiye Klinikleri J Endocrin-Special Topics 2009;2(2):110-2

HIRSUTISM

Hirsutism is defined as an overgrowth of androgen-dependent sexual hair.[1] It is often shown as an increase in midline hair, including the upper lip, chin, cheeks, lower abdomen, back, chest and proximal part of the extremities. Hirsutism is often cited as a hormonal imbalance resulting in excess androgen secretion from the ovary, adrenal, or both, rather than a cosmetic problem. Overgrowth of sexual hair is

due to excessive androgen production, increased androgen sensitivity of hair follicles, or increased conversion of a weak androgen to a more potent androgen.[2] The potential source of increased androgen is the ovaries, adrenal glands, exogenous hormones, and other drugs.

HIRSUTISM TREATMENT PROTOCOLS

For women with mild hirsutism with normal menstrual cycles, only psychological relief is sufficient. Women with moderate or severe hirsutism with menstrual irregularities require treatment. Medical treatments that include adrenal or ovarian suppression or block the peripheral androgen effect are recommended for women who do not want to have children in the near future.[3] If the major problem is infertility, an appropriate approach after an appropriate ovulation induction [e.g., clomiphene, bromocriptine, human menopausal gonadotropin (hMG)] or gonadotropin-releasing hormone (GnRH) are initiated.[4] Medical treatment is not completely successful. It has been reported that response is obtained between 23% and 95% depending on the drug use and dose.[5] The most commonly used drugs in treatment are combined oral contraceptives, GnRH analogs, androgen receptor antagonists, and corticosteroids. These drug treatments act by (1) reducing androgen production; (2) increasing the metabolic breakdown of androgens; (3) inhibiting androgen receptors; (4) inhibiting enzymes in the peripheral production of testosterone or dihydrotestosterone; (5) increasing SHBG.[5]

FLUTAMIDE

Flutamid is a strong, highly selective, non-steroidal pure peripheral antiandrogen with no hormonal or antigonadotropic effects and does not cause menstrual irregularity. Although its exact mechanism is unknown, it reversibly inhibits androgen receptors in the target tissue.[6] Flutamide has been used in high doses (500-750 mg/day) in the treatment of benign prostatic hyperplasia and prostate adenocarcinoma. Its safety in pregnancy is not known, and it can cause ambiguous genitalia in males in a study conducted on rats. Flutamide therapy should be combined with contraception in married women. In many studies, flutamide has been used at doses of 500-750 mg/day in the treatment of hirsutism. When used at these doses, a high rate of liver toxicity was observed, and because it is an expensive drug, it is difficult to be preferred in treatment due to its high cost. However, in studies conducted in recent years, 250 mg/day flutamide intake has been shown to be an effective treatment in controlling severe hirsutism, and it has a similar effect on hair growth compared to 500 mg/day flutamide use.[7,8] In fact, it has been found that using a lower dose of 125 mg/day flutamide is more reliable and cost effective than high doses such as 250-750 mg/day.[9] It has also been shown in another study that 62.5 mg/day can be used in a well-tolerated manner in the treatment of hirsutism without showing any hormonal changes and liver toxicity or other gastrointestinal side effects. Flutamide has also been used to treat acne. Acne affects more than 40 million women, more than half of them over the age of 25. Acne is a cosmetic problem, especially in young women, causing psychosocial problems.[11] In a recent study, flutamide was used at doses of 62.5 mg/day for the treatment of acne and hirsutism in adolescent girls. In patients with hyperinsulinemia, flutamide 62.5 mg/day and metformin treatment were added. As a result of this study, it is recommended to use low-dose flutamide in adolescent girls for cosmetic purposes. In terms of cost, it is considerably cheaper than using high-dose flutamide.[12] The use of flutamide as low as 250 mg/day has been found to be more effective and easily tolerated in hirsutism than another antiandrogen, 5α-reductase inhibitor finasteride.[13] Side effects include decreased appetite, amenorrhea, decreased libido, and dry skin. A rare but serious side effect is hepatotoxicity. Therefore, liver function tests should be followed closely during treatment. In studies on hepatotoxicity, when flutamide is used in high doses (500-1500 mg/day), hepatotoxicity occurs, liver toxicity is rarely observed when low-dose flutamide (doses of 250 mg/day or less) is used.[14-16]

Since flutamide is a selective antiandrogen, it has no progestogenic, estrogenic, corticoid, or gonadotropic effects.[17] No changes in ovarian or adrenal androgen levels have been reported in long-term treatments.[18] It has also been used with drugs such as flutamide, finasteride, metformin, pioglitazone, and oral contraceptives in the treatment of hirsutism.[19]

It was emphasized that in patients using flutamide with metformin, ovulation was induced and the treatment should be discontinued due to the embryotoxicity of flutamide when pregnancy occurs. In conclusion, flutamide therapy can be used as a beneficial and effective choice for resistant hirsutism cases, and liver enzymes should be followed in patients using drug therapy.

BICALUTAMIDE

Bicalutamide is a new, effective, well tolerated, non-steroidal, pure antiandrogen with a half-life of 7-10 days.[20] This antiandrogenic drug is used in the treatment of prostate cancer and hirsutism.[21,22] In the treatment of early stage prostate cancer, 50-400 mg/day was used in addition to surgical and medical castration, while 25 mg/day was used in hirsutism.[22] In the study conducted by Müderris et al., the daily use of 25 mg bicalutamide did not affect the lipid profile, liver or renal functions, or hormone profile during the controls performed at intervals of 3-6 months. It has been found to be effective in hirsutism.[22] No changes in ovarian or adrenal androgen levels have been reported with bicalutamide therapy, as with flutamide.[20,22] Rarely, side effects such as hot flashes, diarrhea, nausea, fatigue, and itching have been reported with prolonged therapy. The most important side effects are elevated liver enzymes and jaundice.[21] During the treatment of hirsutism, bicalutamide has not been reported any side effects, including menstrual irregularity.[22] There are only two studies in the literature on bicalutamide treatment in hirsutism. Because bicalutamide treatment is very expensive, cheaper treatment alternatives are preferred in the treatment of hirsutism. However, if it is used in low doses, it can be a more economical treatment. Bahçeci et al. also investigated the effect of bicalutamide treatment on insulin resistance and hirsutism. They emphasized that low-dose bicalutamide is an effective drug in the treatment of hirsutism and not effective on insulin resistance.[23]

As a result, when bicalutamide is used in low doses in the treatment of hirsutism, it is both effective in terms of treatment and economical in terms of cost, but if the patient has polycystic ovary syndrome and insulin resistance, insulin sensitizing drugs should be added to bicalutamide treatment.

REFERENCES

1. Ehrmann DA, Rosenfield RL. Clinical review, an endocrinologic approach to the patient with hirsutism. J Clin Endocrinol Metab 1990; 71(1):1-4.
2. Biffignandi P, Massucchetti C, Molinatti GM. Female hirsutism: Pathophysiological considerations and therapeutic implications. Endocr Rev 1984;5(4):498-513.
3. Hock DL, Seifer DB. New treatments of hyperandrogenism and hirsutism. Obstet Gynecol Clin North Am 2000;27(3):567-81, vi-vii.
4. Fruzzetti F, Bersi C, Parrini D, Ricci C, Genazzani AR. Treatment of hirsutism: comparisons between different antiandrogens with central and peripheral effects. Fertil Steril 1999; 71(3): 445-51.
5. Pazos F, Escobar-Morreale HF, Balsa J, Sancho JM, Varela C. Prospective randomized study comparing the long-acting gonadotropinreleasing hormone agonist triptorelin, flutamide, and cyproterone acetate, used in combination with an oral contraceptive, in the treatment of hirsutism. Fertil Steril 1999;71(1):122-8.

6. Simard J, Luthy I, Guay J, Belanger A, Labrie F. Characteristics of interaction of the antiandrogen flutamide with the androgen receptor in various target tissues. Mol Cell Endocrinol 1986; 44: 261-70.
7. Müderris II, Bayram F, Sahin Y, Keleştimur F, Tutuş A, Ayata D. The efficacy of 250 mg/day flutamide in the treatment of patients with hirsutism. Fertil Steril 1996; 66 (2): 220-2.
8. Müderris II, Bayram F, Sahin Y, Keleştimur F. A comparison between two doses of flutamide (250 mg/d and 500 m/d) in the treatment of hirsutism. Fertil Steril 1997; 68 (4): 644-7.
9. Müderris II, Bayram F. Clinical efficacy of lower dose flutamide 125 mg/day in the treatment of hirsutism. J Endocrinol Invest 1999; 22 (3): 165-8.
10. Müderris II, Bayram F, Güven M. Treatment of hirsutism with lowest-dose flutamide (62.5 mg/day). Gynecol Endocinol 2000; 12 (1): 38-41.
11. Müderris II, Bayram F, Güven M. A prospective, randomized trial comparing flutamide (250 mg/d) and finasteride (5 mg/d) in the treatment of hirsutism. Fertil Steril 2000; 73 (5): 984-7.
12. Erenus M, Gürbüz O, Durmuşoğlu F, Demirçay Z, Pekin S. Comparison of the efficacy of spironolactone versus flutamide in the treatment of hirsutism. Fertil Steril 1994; 61(4):613-6.
13. Couzinet B, Pholsena M, Young J, Schaison G. The impact of a pure antiandrogen flutamide on LH, FSH, androgens and clinical status in idiopathic hirsutism. Clin Endocrinol (Oxf) 1993;39(2):157-62.
14. George R, Clarke S, Thiboutot D. Hormonal therapy for acne. Semin Cutan Med Surg 2008;27(3):188-96.
15. Pizzo A, Borrielli I, Mastroeni MT, Fattori A, Dugo C, Dugo N, et al. Low-dose flutamide in the treatment of hyperandrogenism in adolescents Minerva Pediatr2008;60(6):1357-66.
16. Dikensoy E, Balat O, Pence S, Akcali C, Cicek H. The risk of hepatotoxicity during long-term and low-dose flutamide in hirsutism. Arch Gynecol Obstet 2009;279(3): 321-7.
17. Castelo-Branco C, Moyano D, Gómez O, Balasch J. Long-term safety and tolerability of flutamide for the treatment of hirsutism. Fertil Steril 2009;91(4):1183-8.
18. Calaf J, López E, Millet A, Alcañiz J, Fortuny A, Vidal O, et al. Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: a 12-month, double-blind, parallel clinical trial. J Clin Metab Endocrinol 2007;92(9):3446-52.
19. Ibáñez L, López-Bermejo A, del Rio L, Enríquez G, Valls C, de Zegher F. Combined low-dose pioglitazone, flutamide, and metformin for women with androgen excess. J Clin Endocrinol Metab 2007;92(5):1710-4.
20. Furr BJ. The development of Casodex (bicalutamide): preclinical studies. Eur Urol 1996;29 Suppl 2:83-95.
21. Tyrell CJ. Tolerability and quality of life aspects with the antiandrogen Casodex monotherapy for prostate cancer. Eur Urol 1994;26 Suppl 1:15-9.
22. Müderris II, Bayram F, Özcelik B, Güven M. New alternative treatment in hirsutism: bicalutamide 25 mg/day. Gynecol Endocrinol 2002;16(1):63-6.
23. Bahceci M, Tuzcu A, Canoruc N, Tuzun Y, Kidir V, Aslan C. Serum C-reactive protein (CRP) levels and insulin resistance in non-obese women with polycystic ovarian syndrome, and effect of bicalutamide on hirsutism, CRP levels and insulin resistance. Horm Res 2004;62(6):283-7.