How actual is the treatment with antiandrogen alone in patients with polycystic ovary syndrome?

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INTRODUCTION

Women with of polycystic ovary syndrome (PCOS) usually seek medical attention to ameliorate the effects of androgens on appearance, on fertility, and less often for prevention of metabolic complications.

This condition affects 5-10% of women in reproductive age (1, 2). Despite the fact that scientific knowledge in the pathogenesis of this syndrome has advanced considerably, its cause remains unknown (3). Abnormalities in steroidogenesis and metabolism are both present to a different degree, but their causative relationship remains unresolved (4). The debate about the primary role between hyperandrogenism and hyperinsulinemia in PCOS, continues because there are well designed controlled studies in support of either view (5-7). The translation- however, of these complicated intellectual pathogenetic mechanisms, to therapeutic approach and clinical practice has not kept pace, and so far there is no established single therapy for all aspects of this syndrome (8). Today the most accepted therapeutic approach is directed to the identified manifestations requiring treatment. Nevertheless some new therapeutic modalities are the results of this continuous research (9, 10).

As androgens excess and hyperinsulinemia contribute each one to a different degree on this syndrome, therapeutic efforts have been focused to agents which could treat or modify both cluster of clinical manifestations. Current therapeutic efforts are trying to kill two birds, manifestations of hyperandrogenemia and hyperinsulinemia, with one stone either insulin sensitizers or antiandrogens (11, 12).This goal is only partially achieved, until to date, using either medication of these two major groups, as monotherapy (10, 13).

Antiandrogens are considered the treatment of choice for the "visible" manifestations of the skin, hirsutism and acne (14, 15).There is no agreement, however, to which degree antiandrogens correct the "hidden" ovarian dysfunction manifested as chronic anovulation and the "invisible" manifestations, of the metabolism like hyperinsulinemia, insulin resistance, dyslipidemia etc. Since the etiology of the syndrome remains unknown and only theories are available trying to explain different groups of symptoms and signs, the therapeutic approach is also till today symptom-oriented.

None of the pathogenetic (3) mechanisms proposed is sufficient to account by itself for the whole group of hormonal and metabolic disturbances. Antiandrogen alone or more often in combination with oral contraceptives (OC) is the most accepted type of therapy in skin manifestations of PCOS (14, 15). Nevertheless recently monotherapy with these agents, either by reducing androgens levels or by inhibiting androgen action, has been tried to control the whole spectrum of the syndrome, with variable degree of response (10, 12, 13).

ANTIANDROGENS

Antiandrogens, or androgen antagonists, are defined as compounds that interact with the androgen receptor (AR) and thus preventing the biologic action of androgens on their target tissue (16).

Steroidal antiandrogens

Most compounds used as antiandrogens were developed for other purposes and later found to have antiandrogenic activity. None is labeled for use in treatment of androgenic disorder in women.

Spironolactone

The oldest of these is spironolactone (SP), originally developed as an aldosterone antagonist. Antiandrogenic properties of SP have been demonstrated in various experimental systems and its efficacy in androgenic disorders, especially hirsutism is well established so that it is widely used for this purpose (16). Orally administered SP is rapidly absorbed and reaches maximal plasma within 30-60 minutes. Although most of the administered dose is excret-

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ed in the urine and feces, the enterohepatic route plays a considerable role in the delay of the elimination of this compound. Intake of food promotes absorption of SP and possibly decreases its first-pass metabolism. Canrenone, a weak antiandrogen, has been identified as a major metabolite of spironolactone (17).

Spironolactone also interacts with other steroid receptors and with steroidogenic enzymatic systems. In particular, SP has some progestational and possibly partial antiestrogenic activities (18, 19). It also diminishes androgen biosynthesis in the gonads and in adrenal steroid-producing cells by decreasing the microsomal cytochrome P-450 content (20). Furthermore, SP has a direct inhibitory effect on 5α-reductase (21).

The value of SP in the treatment of hirsutism has been well documented (22, 23). Furthermore, SP improves acne and seborrhea (24, 25). Beneficial effects of SP on hirsutism have been documented at doses as low as 50 mg/day (administered between days 4 and 22 of each menstrual cycle) (25). This regimen results in an improvement of hirsutism in 3-8 months. For patients with moderate to severe hirsutism, administration of higher doses of SP (200 mg/day) resulted in decreases in the density, diameter, and the rate of hair growth within 2 months (26).

Therapy with SP results in a decrease in serum concentrations of total and free testosterone without significant alterations in the levels of LH, FSH, estradiol, progesterone, DHEAS, and cortisol (25, 26). Use of SP may lead to a mild increase in serum triglycerides without affecting the cholesterol level (27). Spironolactone increases aldosterone levels but has no significant effect on serum potassium and sodium concentrations (27). However, in view of potentially dangerous hyperkalemia, SP should not be used in women with renal insufficiency.

Initially, SP administration may cause polyuria, polydipsia, weakness, and fatigue. Diuretic effects are usually limited to the first few days of treatment (26). Long-term side effects of SP are usually minor but may occur often. Occasionally, use of SP may be associated with headaches, increased appetite, and increased body weight, more often breast enlargement and tenderness (26%), and dizziness (26%) (28). In most patients, the above side effects are mild and have no clinical significance. Frequently, patients experience menstrual disturbances (22%).The weak progestogenic activity of SP may be responsible for this complication but, this issue has not been evaluated adequately. Menstrual disturbances were usually well controlled by concomitant use of oral contraceptives (28, 29).

The experience gained with the use of SP suggests that its dosage should be adjusted according to the severity of symptoms (23, 25). In mild to moderate hirsutism, oral SP is often recommended either on a cyclic basis (for example, between days 4 and 22) or daily at the lowest effective dose (50-75 mg) to minimize side effects. In more severe cases, higher dose of oral SP (150-200 mg) are recommended (28). Isolated acne may be treated effectively with topical cream containing 5% SP (30).

In a recent paper lean PCOS women were treated with spironolactone alone for 3-4 months, insulin resistance was partially reversed, although remained higher than in controls and showed no further improvement after 1 year of treatment (12). Menstrual irregularities in PCOS women are either unaffected or more often worsen, with SP treatment alone (28).

In conclusion SP has been used in PCOS women, as monotherapy with good results in skin manifestations and some beneficial effect on insulin mediated glucose disposal. However, its side effects, particularly menstrual irregularities, restrict the treatment to OC combination and limit SP use as monotherapy.

CYPROTERONE ACETATE

Cyproterone acetate (CPA), a progestin with antiandrogenic activity, has been used extensively in Europe for >20 years but not been approved in the United States for this indication (14). It is probably the best established drug for treatment of hirsutism and is also effective against acne (31, 32). One of the best-known steroidal antiandrogens, cyproterone acetate (CPA) is derived from 17-hydroxyprogesterone. Cyproterone acetate blocks androgen action by competitive binding to the AR; it also has significant progestogenic activity and mild glucocorticoid activity (32). Antiandrogenic activity of CPA is surprising because its 17α-acetyl group would not be expected to bind well to AR; typically, good receptor affinity is associated with a free 17α-hydroxyl group (14, 33-35). Cyproterone acetate binds to the AR with about 21% of the affinity of testosterone (12). Oral absorption of CPA is almost complete. Peak plasma concentration after a single oral dose (2 mg) is reached after 3.7±0.8 hours; the post maximum disposition is biphasic, with half-lives of 3.0±1.3 hours and 2.0±0.4 days (36). Cyproterone acetate is very lipophilic, and its long biologic half-life may be explained by its accumulation at high concentrations in fat. The achievement of equilibrium between its administration and elimination may require up to 8 days. The half

time of elimination is prolonged in obese patients. This may explain clinical observations of delayed withdrawal bleeding after discontinuation of treatment in obese women. In hirsute women, CPA attenuates androgen action by blocking AR, as well as by reducing serum testosterone levels (by inhibiting gonadotropin release) and decreasing 5α-reductase activity (36). In women, the main indication for the use of CPA is control of excessive androgenic effects on the pilosebaceous unit. Cyproterone acetate is almost never given alone in patients with polycystic ovarian syndrome, not only to avoid the feminization of a male fetus,a common risk with the other antiandrogens, but furthermore causes menstrual bleeding. So it is usually given with excellent control of hirsutism, seborrhea, and acne in combination with an estrogen (usually ethinyl estradiol) as a contraceptive preparation (37).

A commonly prescribed schedule involves administration of CPA (50-100 mg/day) on days 5-14 of the cycle and ethinyl estradiol (35 mg/day) on cycle days 5-25. This cyclic schedule (reserve sequential regimen), used since 1969, allows regular uterine bleeding, provides excellent contraception, and is effective in the treatment of severe hirsutism and acne (38). Satisfactory results have been obtained with other protocols using a wide range of doses of CPA (2-100 mg/day) in combination with ethinyl estradiol (20-50 mg/day); these preparations were used either continuously or in a cyclic fashion (37, 38, 39).Many physicians prescribe CPA by simply adding a 50-mg tablet to the first 10 days of a birth control cycle. With the above therapeutic regimens, 4-9 months are usually required to improve hirsutism (37, 39). CPA is nearly always given with estrogen, to avoid unpredictable bleeding patterns. When it is used as the progestin in a combination OC, its efficacy against hirsutism has been variable in different reports (40-42).

Its side effects are similar to those of medroxyprogesterone acetate and include weight gain, fluid retention, mood changes, and decreased libido (10%), breast tenderness (30%), and headaches (20%) (43). Some of these side effects are improved by combining CPA with estrogen. The effects of such a combination on the lipid profile are slight and consist of a small increase in total cholesterol; increases in HDL cholesterol, HDL2 cholesterol, and Apo-Al lipoproteins; an increase in the HDL/LDL-cholesterol ratio; and an increase in triglycerides (44). Because of the potential hepatotoxicity of CPA, monitoring of serum transaminases every 3-6 months is recommended. However, to our knowledge, significant hepatotoxicity CPA may has not been reported in women using CPA in a cyclic fashion. Rarely, administration of CPA is associated with adrenal suppression (45). At present, CPA is widely used in Europe and Canada but is not available in the United States.

Non-steroidal antiandrogens

This broad group of drug includes "pure" nonsteroidal antiandrogens such as flutamide as well as other nonsteroidal agents with antiandrogenic properties, such as cimetidine. "Pure" non-steroidal androgen antagonists were developed in the hope of producing drugs with maximized antiandrogenic potency while eliminating the side effects common to steroidal antiandrogens (16). Pure non-steroidal androgen antagonists bind to androgen receptor (AR) with high affinity and it was considered to have virtually no progestational, glucocorticoid, or any other hormonal or antihormonal activity (16).

FLUTAMIDE

Flutamide (Sch 13521;3'-trifluoromethyl-4'-nitro-2-methyl-propinoylanilide) is the best-known nonsteroidal antiandrogen. This non-steroidal antiandrogen has been found to be effective in the treatment of skin manifestations of hyperandrogenemia,acne and hirsutism (28, 45-47). Originally, it was synthesized as a bacteriostatic agent; only subsequently it was found to possess antiandrogenic properties. After oral administration, flutamide achieves a maximum serum concentration at approximately 2 hours. Flutamide itself is a relatively weak antiandrogen; however, upon ingestion it undergoes significant first-pass metabolism to a potent antiandrogen, 2-hydroxyflutamide. 2-Hydroxyflutamide accounts for approximately 23% of the plasma level of flutamide 1 hour after oral intake (47, 48). Steady-state concentrations of 2-hydroxyflutamide were found after 2-4 days of administration of flutamide (250 mg every 8 hours). Both flutamide and 2-hydroxyflutamide inhibit the binding of 5α-DHT to AR and reduce nuclear translocation of the AR (47). The mechanisms of action of flutamide are still incompletely understood (51). The first reports the results were satisfactory in women with hirsutism and acne treated with Flutamide combined with OC. Flutamide as monotherapy in lean and obese PCOS showed that the signs of hyperandrogenism, hirsutism and particularly acne had significantly improved (10). There was no effect on gonadotropin response to GnRH (49, 50), but basal levels of FSH showed a rise associated with a small fall of LH (49, 50). Clinical research the last five years has progressively shown that this agent, as monotherapy, has rather beneficial effects towards the two other

major disturbances of the syndrome, chronic anovulation and to a lesser extent to insulin resistance. Recent work by De Leo et al. (13) showed that treatment with flutamide alone for six months restored ovulatory cycles in all young women with PCOS, ultrasonography also demonstrated normalization of ovarian volume with one dominant follicle.The above findings lead the authors to the suggestion that flutamide inhibits androgen synthesis, through restoration of ovulation, without excluding a direct block of the steroidogenic enzymes of androgen biosynthesis in ovarian theca cells. Although flutamide is considered a pure antiandrogen, it decreases circulating concentrations of DHEAS as well as androstenedione, 3α-androstanediol glucuronide, and DHEAS in young women with PCO (10, 12, 13, 50).These effects may be due to inhibition of adrenal 17-20 lyase (52). Regarding its metabolic effect, Flutamide has not significant (10) or minimal clinically significant (12) effect on insulin resistance. Interestingly it seems to have a beneficial effect on lipid profile in PCOS women with no alteration on insulin sensitivity (53).

In a prospective randomized trial, women with moderate to severe hirsutism were treated with flutamide (250 mg orally, twice a day) or SP (50 mg orally, twice a day) (28). Both groups of patients simultaneously received triphasic oral contraceptives. After 6 months of therapy,it was clearly demonstrated that flutamide is superior to SP and better tolerated.

In most studies, no serious adverse effects have been observed during short-and long-term treatment with flutamide (28, 48, 45). Its use is associated with a greenishbluish discoloration of the urine. The most common side effect is skin dryness, noted in 75% of patients (28). Elevated levels of liver transaminases have been reported in up to 32% of patients; however, clinically significant liver toxicity is rare. Cases of cholostatic hepatitis and even fatal liver failure have been reported in patients treated with flutamide (54, 55).

FINASTERIDE

Finasteride belongs to a recently developed class of 5α-reductase inhibitors. Because finasteride does not block androgen actions at the receptor level, it does not fully comply with the definition of antiandrogens. However, finasteride inhibits the actions of androgens by decreasing the production of 5α-DHT, the most potent ligand for AR (56).

In patients treated with high doses of finasteride (100 mg/day), the serum 5α-DHT reduction did not exceed 70%-80%, suggesting that this inhibitor may not completely block 5α-reductase activity in humans (56). In light of the evidence that there are at least two 5α-reductase isoenzymes, (56) it is possible that finasteride selectively inhibits only one of these isoenzymes, and thus is unable to suppress 5α-DHT production completely. This suggestion is further supported by the observation that administration of finasteride to males with benign prostatic hyperplasia does not decrease the sebum score from baseline values (*i.e.*, the isoenzyme of 5α-reductase present in the sebaceous gland may not be affected by finasteride).

Most of the experience with finasteride so far has been accumulated from patients with benign prostatic hypertrophy (56). Recently, some studies have evaluated this drug in the treatment of hirsute women. Finasteride was administrated for 3 months (5 mg/day orally), with a resultant significant decrease of the Ferriman-Gallwey score of hirsutism. Finasteride treatment had no significant effect on the levels of circulating testosterone and gonadotropins. Finasteride alone is an actual treatment for skin manifestations in women with PCOS with a variable degree of response.

Other drugs with some degree of antiandrogenic activity (57), include the histamine-2 blocker cimetidine (58) (although its efficacy in hirsutism is not entirely clear) and the antifungal agent ketoconazole, which is quite effective. Ketoconazole, some preliminary studies, had shown that PCOS women treated with it as monotherapy, besides the impressive results on hirsutism and acne, had also some beneficial effect in glucose intolerence, without any alteration of the menstrual disturbances. Ketoconazole however has no place in PCOS therapy either alone or in combination and is considered inappropriate for long-term treatment for benign condition because can cause serious liver toxicity and suppresses cortisol production as well.

CONCLUSIONS

Most hyperandrogenic women cannot be cured but can be successfully treated. Currently available treatments focus on control of symptoms and require long-term pharmacotherapy that blocks the production and/or the effects of androgens. Actions of androgens may be inhibited by several mechanisms; blocking of the AR, decreasing the synthesis of androgens, and decreasing the metabolism of androgens to the most potent AR ligand, 5α-DHT. Clinically available antiandrogens may evoke any or all of these mechanisms. Antiandrogens alone provide a logical and clinically effective pharmacotherapy for hirsutism, acne, seborrhea, and androgen-induced hair loss. Furthermore, for the first time, the treatment with the antiandrogens alone in

recent reports gives promising results, for the metabolic and ovulatory abnormalities associated with the PCOS. Both steroidal and non-steroidal antiandrogens-however, may cause significant adverse effects, and even when these medications are well tolerated, improvement of symptoms may not be adequate. Generally the ABC rule of antiandrogen treatment still valid is that: A) it is a long-term treatment, B) discontinuation is associated with variable degree of recurrence of symptoms and signs of hyperandrogenism and C) all antiandrogens pose a risk to the fetus, reliable contraception and appropriate counseling are essential. At the moment there is no antiandrogen to be used safely and effectively, in clinical practice as monotherapy for all aspects of PCOS, but for skin manifestations the treatment with antiandrogens alone it is currently an actual one.

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