



Use of spironolactone in treatment of hirsutism

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■ Spironolactone (Aldactone), 100 mg to 200 mg daily, has antiandrogenic effects that may enhance treatment of androgen-excess syndromes, particularly severe hirsutism. Combination therapy with an oral contraceptive or with dexamethasone appears to have a beneficial effect. Side effects are transient. The drug should be avoided during pregnancy and in women who have a family history of breast cancer, although there is no proven association between spironolactone and breast malignancy.

□ INDEX TERMS: ANDROGEN EXCESS; HIRSUTISM; SPIRONOLACTONE □ CLEVE CLIN J MED 1990; 57:285-287

SPIRONOLACTONE (Aldactone) has received considerable attention over the past 10 years as a treatment for androgen-excess syndromes, particularly hirsutism. Synthesized as an aldosterone antagonist,¹ spironolactone has been used extensively as a salt-wasting diuretic and antihypertensive, but the drug clearly has other effects. In men treated with high doses, it may cause gynecomastia, breast tenderness, decreased libido, impaired sperm production, and impotence.² In women, menstrual irregularities and amenorrhea have been reported.²

Hirsutism is linked to increased production and bioavailability of androgen and its increased utilization by hair follicles. Although potentially lethal causes of hyperandrogenism do exist, for most women with excess facial and body hair, the problem is benign, mild, and can be corrected with physical removal. Medical therapy

such as spironolactone is best reserved for more severe cases of hirsutism.

This paper delineates what is known about the mechanism of action of spironolactone in the treatment of androgen-excess disorders and recommends strategies for its use, based on clinical observations and investigations.

SPIRONOLACTONE AND THE REPRODUCTIVE SYSTEM

Spironolactone influences androgen activity in several ways that may decrease hair growth and other androgen-induced abnormalities. The clinical observation that spironolactone produces antiandrogenic effects in men was followed by reports that it interfered with testosterone production.³ It also functions as an androgen receptor antagonist that is equipotent with dihydrotestosterone (DHT) at tenfold higher concentration.⁴

In women, spironolactone decreases the rate of testosterone production, increases its metabolic clearance, and reduces circulating testosterone and androstenedione levels without affecting the adrenal androgens, dehydroepiandrosterone sulfate (DHEAS) and dehydroepiandrosterone (DHEA).^{5,6} Spironolactone also

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may interfere with binding of testosterone to sex hormone-binding globulin (SHBG); consequently, the percent of unbound and nonspecifically bound testosterone increases, but absolute levels decline.⁷ Aromatase activity is unchanged.⁸ Peripheral 5- α reductase activity, usually increased in hirsutism, is decreased by spironolactone therapy but not to normal levels.⁹ Despite decreased 5- α reductase activity and blockade of the DHT receptor, there is increased conversion of DHT to its degradation product, 3- α diol-G.¹⁰

RESPONSE OF HIRSUTISM TO SPIRONOLACTONE

The first observation of a spironolactone effect on hirsutism was by Ober and Hennessy, who reported an incidental effect in a patient being treated for hypertension.¹¹ Boisselle and Tremblay reported their subjective impressions—no further progression of coarsening and darkening of hair, slowed growth rate of existing hair, and decreased hair shaft diameter—from six women taking spironolactone, 25 mg bid, for 6 months.⁵ Shapiro and Evron used the Ferriman and Gallwey scoring system to evaluate the effects of spironolactone, 100 mg bid, from day 4 to day 22 of each menstrual cycle.¹² Improvement was recorded in 23 of the 30 women in the trial. Mean Ferriman and Gallwey score declined to 64% of the baseline values and the quality of hair improved, becoming finer and softer.

Various methods have been used to document the effect of spironolactone on hirsutism. Cumming and associates used an optical micrometer to obtain an unbiased measure of hair shaft diameter, reduced because of the antiandrogenic effect.⁶ Clinical scales of density and distribution of facial hair also demonstrated a clear beneficial effect in 19 of 20 women with generally severe hirsutism. The clinical efficacy of spironolactone has been confirmed by other investigators as well, using various dosages and measures of benefit; for example, Messina and associates, 400 mg/d and Ferriman and Gallwey score;¹³ Nelson, 50 mg/d and frequency of physical removal of excess hair;¹⁴ Milewicz and associates, 100 mg/d and decreased Lorenzo score;¹⁵ and Lobo, 100 mg/d and 200 mg/d and hair shaft diameter.¹⁰

In contrast, Dorrington-Ward and associates, using 150 mg/d, Ferriman and Gallwey scores, hair shaft diameter, and length,¹⁶ found no significant change.

COMBINED THERAPY FOR HIRSUTISM

The combination of other drugs with spironolactone appears to have a beneficial effect. Blum and associates

reported decreased hair growth following combined spironolactone and bromocriptine therapy in two women with polycystic ovarian syndrome.¹⁷ No objective scoring systems were used. Chapman and colleagues found that the combination of spironolactone, 100 mg/d, and a birth control pill containing 30 μ g ethinyl estradiol and 2 mg ethynodiol diacetate (Demulen 30) was superior to their previously poor results with spironolactone alone.¹⁸ In a similar study, Pittaway and colleagues evaluated two regimens—50 μ g to 80 μ g ethinyl estradiol plus 1 mg norethindrone or 0.5 mg dexamethasone—in combination with spironolactone.¹⁹ With both regimens, the intervals increased between physical treatments of hair growth. Although some clinicians may wish to advise patients taking dexamethasone to wear identification bracelets, the risks of physiologic suppression appear to be minimal.

RESPONSE OF OTHER ANDROGEN-INDUCED CHANGES

Evron and Shapiro suggested that spironolactone could correct hyperandrogenic anovulation, but others have not substantiated their findings.²⁰ This is not a desirable use for spironolactone because of possible antiandrogenic effects on the fetus and the ease of ovulation induction with other means. Several studies have mentioned incidental improvement in acne. Frontal and other male pattern baldness has not been extensively investigated but there is anecdotal evidence of benefit. At present, other forms of therapy, such as topical minoxidil, are preferable.

SIDE EFFECTS OF SPIRONOLACTONE

Pharmacological reference works list a forbidding array of potential side effects for spironolactone, many of which are short-lived if they occur at all. The diuretic effect tends to be transient and there is little chance of hypotension in normal individuals. Electrolyte imbalance has not been reported, even with high-dose treatment of hirsutism, although the patient should avoid excessive potassium consumption. Lethargy and stomach upset occur occasionally. Menstrual irregularity can be a problem, particularly in women who have a history of irregularity, but this is usually transient. In most patients, a reasonably regular, although anovulatory, cycle develops. Persistent irregularity can be corrected by using spironolactone in a 21 day on/7 day off regimen or, preferably, by combining it with an oral contraceptive.

There is concern that spironolactone, like many

other gestagens, may stimulate the breast and possibly cause breast cancer. Carcinoma of the breast has been reported in patients taking spironolactone for reasons other than treatment of hirsutism; there is no evidence that spironolactone causes breast tumors, but neither can it be proven that it does not contribute to the development of breast malignancy. Patients should be so informed, and should not be treated with spironolactone if there is a strong family history of breast malignancy.

The drug should be not be used in pregnancy and should be used with adequate contraception in reproductive-age patients. There have been no reports of antiandrogenic effects developing as a result of maternal spironolactone therapy early in pregnancy, but such a development is unlikely since the pregnancy should be diagnosed before embryogenesis of the reproductive tract.

TREATMENT RECOMMENDATIONS

The present dosage recommendations for spironolactone are 100 mg to 200 mg daily in two divided doses, alone or in combination with 35 µg ethinyl estradiol and 0.5 mg norethindrone, or with 50 mg ethinyl estradiol and 1 mg ethynodiol diacetate. An alternative strategy is spironolactone in combination with dexamethasone, 0.25 mg to 0.5 mg at bedtime, which is below the physiologic threshold for immunosuppression.

The combination of spironolactone with a birth control pill or dexamethasone is probably the best available therapy for severe hirsutism, although it is not approved for this indication in the United States. Physical methods of hair removal are effective and should not be overlooked during treatment, and patients with mild hirsutism should be discouraged from medical treatment.

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