# Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone

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***Background:*** The use of either oral contraceptives or antiandrogens has been shown to be helpful in the treatment of women with acne.

***Objectives:*** We investigated the safety and efficacy of acne treatment using both spironolactone and a combined contraceptive containing drospirenone.

***Methods:*** Twenty-seven women with either severe papular or nodulocystic facial acne were treated with a combined oral contraceptive containing 30 $\mu$g ethinyl estradiol and 3 mg drospirenone (EE/DRSP; Yasmin) and spironolactone (SL) 100 mg taken daily. A serum potassium level was obtained before initiation of therapy. Between 4 and 6 weeks after the start of both medications, a second serum potassium level was obtained. Side effects were recorded.

***Results:*** No significant elevation of serum potassium was found in any of the subjects nor were there any reported additional side effects significant enough to discontinue treatment. At follow up, 85% of subjects were entirely clear of acne lesions or had excellent improvement, 7.4% were mildly improved, and 7.4% were not improved.

***Limitations:*** This was a small prospective study.

***Conclusion:*** The combination of EE/DRSP and SL 100 mg daily appears to have efficacy and is well tolerated in the treatment of severe papular and nodulocystic acne in women. (J Am Acad Dermatol 2008;58:60-2.)

Androgens play a significant role in the etiology of acne.[1] Findings that suggest significant hormonal influence in female acne include the appearance of acne at menarche with associated increase in sebum excretion, occurrence of premenstrual flares, and the association of acne with hirsutism and ovarian cysts. Therefore many approaches for treating acne in women have attempted to decrease androgen activity. Several studies have demonstrated that combined oral contraceptives (OC) can be an effective treatment for acne in women.[2-5] Recent epidemiological studies from Denmark suggest that use of OC appears to be associated with a reduced prevalence of acne in adolescent girls.[6] The antiandrogen effects of OC are due to a reduction of ovarian androgen production (due to inhibition of follicle-stimulating and luteinizing hormones) and a decrease in circulating testosterone (due to elevating sex hormone–binding globulin). In addition, some progestogens, such as norgestimate and dienogest,[7] were shown to have 5$\alpha$-reductase inhibitory activity. The recent

*Abbreviations used:*

DRSP: drospirenone
EE: ethinyl estradiol
OC: oral contraceptives
SL: spironolactone

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development of OC containing drospirenone (DRSP), a progestogen with significant antiandrogenic and anti-mineralocorticoid activity, represents an advance over previous combinations.[8] In addition to its capacity for acting as an antiandrogen, DRSP is also nonandrogenic.[9]

Another approach in the treatment of acne is the use of spironolactone (SL), a medication which blocks androgen receptors. Higher doses of SL (100-200 mg daily) have been shown to be very effective in treating acne in women.[10-13] However, 91% of patients in one study experienced side effects including menstrual irregularities and central nervous system side effects (ie, headache and dizziness) when treated with 200 mg of SL daily.[14] A recent study revealed that lower doses of SL (50-100 mg daily) could also be effective in the treatment of acne and were much better tolerated.[15] The main side effect reported at this dosage was mild, clinically insignificant elevation of serum potassium levels.[16]

Many women with severe hormonally mediated facial acne can be recalcitrant to treatment. An ideal treatment should optimize antiandrogenic activity and minimize troublesome side effects. Since elevation of SL dose is associated with an increase in side effects, this is not an optimal treatment strategy. It would be very useful to be able to augment antiandrogen activity without increasing the dose of SL. Ethinyl estradiol/drospirenone (EE/DRSP) is a logical candidate for this purpose, since EE is combined with a derivative of 17$\alpha$-spironolactone. However, since DRSP has many similarities to SL, it is possible that a combination of these two medications might lead to an increase in side effects, including elevation of serum potassium levels. In this study, 27 women were given a combination of EE/DRSP and SL 100 mg daily and monitored for side effects.

## PATIENTS AND METHOD

Our study included female patients with either severe papular or nodulocystic facial acne seen in outpatient settings from 2002 to 2006, who had previously failed to respond to at least one previous standard acne treatment, including 8 patients in whom acne recurred after isotretinoin treatment. The protocol was reviewed and approved by a hospital institutional review board. Twenty-seven women, ages 18 to 43 (mean age, 27.4 years of age), with severe papular or nodulocystic facial acne were treated with oral SL 100 mg daily, plus OC containing 30 $\mu$g of EE and 3 mg of DRSP (Yasmin). Both medications were initiated simultaneously at the beginning of the study and given as a single morning dose. Patients were allowed to continue topical antiacne medications from the prestudy period. Serum potassium levels were drawn before the initiation of the therapy. A second serum potassium level was obtained 4 to 6 weeks after starting these medications and the patients were evaluated for improvement of severity of acne and side effects (spotting, menstrual irregularities, weight gain, and mood changes). None of the patients had pretreatment hyperkalemia, diabetes mellitus, liver or kidney disease, or a history of other drugs that may increase potassium levels.

## RESULTS

All subjects tolerated the combination of these two medications. No subjects reported significant spotting, weight gain, menstrual cycle irregularities, or other side effects severe enough to require discontinuation of either of these medications. Patients were followed up over a period of 6 months. Serum potassium levels ranged from 3.8 to 4.8 mmol/L, with a mean of 4.35 at follow-up (reference range, 3.5-5.3 mmol/L). At the conclusion of the study, 3 patients (11%) were entirely clear of acne lesions, 20 patients (74%) had excellent improvement ($\geq$75% clearance), 2 patients (7.4%) had mild improvement ($\geq$25% clearance), and 2 patients (7.4%) had no change in the clinical appearance.

## DISCUSSION

Despite advances in acne treatment, a significant number of women suffer from severe papular or nodulocystic facial acne. Many patients fail to respond to standard therapies and have a strong cyclical acne pattern, suggesting hormonal mediation. Both EE/DRSP and SL have been useful for treatment of these patients because of their nonandrogenic and antiandrogenic activity. Recent studies have demonstrated that EE/DRSP is superior to a triphasic oral contraceptive containing 35 $\mu$g EE and 0.180, 0.215, and 0.250 mg norgestimate (OrthoTri-Cyclen) in the treatment of acne vulgaris.[8] In addition, EE/DRSP has been shown to be comparable in efficacy to a combined medication containing 35 $\mu$g EE and 2 mg cyproterone acetate (Diane-35) in the treatment of acne, and EE/DRSP also induced reduction of sebum production and facial hair.[4] The superior activity of EE/DRSP against acne has been theorized to be due to the antiandrogenic spironolactone-like effect of the non-androgenic DRSP.

Although spironolactone in dosages above 100 mg daily is efficacious in the treatment of female acne, there are significant side effects.[12] Lowering the daily dose of SL to between 50 and 100 mg improved tolerance but retained adequate clinical efficacy in only one third of treated individuals.[13] Therefore, for women with more recalcitrant acne, it

would be desirable to find a way of optimizing antiandrogen activity without increasing SL to dosages yielding more side effects. Recent studies from European literature also emphasized the need for higher antiandrogen doses (25-50 mg of cyproterone acetate—not currently available in the United States) for persistent control of moderate to severe acne in women.[14]

DRSP, a non-androgenic and non-estrogenic steroid derived from 17$\alpha$-spironolactone, has both anti-aldosterone and anti-androgenic properties. The anti-aldosterone activity of 3 mg DRSP is approximately equivalent to 20 to 25 mg of spironolactone.[17] The high affinity of DRSP to bind to aldosterone receptors decreases potential estrogen side effects, such as weight gain, increased blood pressure, and mood changes. The addition of EE/DRSP to acne treatment with SL would be expected to augment anti-androgen activity but could also potentially increase troubling side effects, such as an increase in serum potassium level. On the other hand, addition of EE/DRSP would be expected to eliminate other side effects of SL, such as menstrual irregularities and spotting. It has been shown that DRSP has an activity profile that is closer to that of natural progesterone than that of any other synthetic progestin.[15]

In this study, 27 women with facial acne showed no side effects severe enough to cause cessation of treatment when treated with EE/DRSP plus SL 100 mg daily. Serum potassium levels after 4 to 6 weeks of treatment were normal, ranging from 3.8 to 4.9 mmol/L, with a mean of 4.35. The combination of these two medications resulted in entirely clear skin or excellent improvement of acne in 85% of subjects during the follow up period.

In conclusion, the combination of low-dose SL with EE/DRSP in the treatment of severe papular and nodulocystic facial acne in women appears to have efficacy and is well tolerated. The augmentation of the anti-androgenic effect of DRSP by SL and the reduction of side effects (such as spotting, menstrual irregularities, weight gain, and mood changes) makes the combination of SL and EE/DRSP attractive for control of moderate to severe, hormonally influenced female acne. However, we recommend that our results be confirmed with a larger series of patients.

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