

Spironolactone and Topical Retinoids in Adult Female Cyclical Acne

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ABSTRACT

Purpose: To access the efficacy of spironolactone and topical retinoids in the treatment of female cyclical acne.
Methods: A retrospective chart review on 41 female patients age 19-57 years old with cyclical acne was performed. Patients were examined over the course of 2 to 102 months while taking 50 to 200mg of spironolactone and topical tretinoin 0.025% or adapalene 0.1% cream. All were diagnosed with acne rated mild to severe, prior to treatment, and were started on an initial dose of 50mg po daily. If significant improvement was not seen within the first 3-6 months, the dose was either held or increased in 25mg increments every 3 months. Patients on oral and topical antibiotics, as well as patients on photodynamic therapy were excluded from the study. The response to treatment was rated on a 0-4 scale with 0 being no response and 4 corresponding to clear skin.
Results: One patient (2.4%) had no response to treatment. This patient was only on 50mg po daily for only 2 months. Only 5 (12.2%) patients had minimal response to treatment and 9 (22.0%), 12 (29.3%), and 14 (34.1%) had a good, excellent, or clear response respectively. The study showed 26 (63.4%) women on treatment with spironolactone and topical retinoids had an excellent or clear outcome, and 35 (85.4%) were considered to have a good, excellent, or clear response.
Conclusion: The addition of spironolactone to topical retinoid treatment suggests a superior response to retinoids alone in clearance of female adult cyclical acne.

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INTRODUCTION

Spironolactone was developed as a mineralocorticoid receptor antagonist following the observation that spirolactones block the effect of mineralocorticoids in the late 1950's. The resulting increase in salt and water excretion led to spironolactone's approval by the US Food and Drug Administration for management of congestive heart failure, cirrhosis of the liver, nephrotic syndrome, essential hypertension, hypokalemia, and primary hyperaldosteronism.[1] Additionally, over the past three decades, spironolactone's effects outside the distal renal tubule have led to dermatologic uses in treatment of androgen mediated conditions, including acne, hirsutism, and alopecia.

Pharmacology

Pharmacokinetics

Spironolactone is formulated as a tablet without a readily available intravenous form because of the drug's poor aqueous solubility.[2] Spironolactone is partially absorbed, with oral bioavailability estimated to be in the 65-90% range.[2,3] Food increases the bioavailability of the drug, however the therapeutic impact of this effect remains unknown.[2] Spironolactone undergoes rapid hepatic metabolism, and more than 90% of available drug is protein bound.[1] Multiple metabolites, including 7α-methylspironolactone, 6β-hydroxy-7-α-methylspironolactone, and canrenone, are formed and also have therapeutic effects. The half-life of spironolactone is estimated to be 1.4 hours, however, the half-lives of its metabolites are much longer. Canrenone, for instance, has a half-life of 16.5 hours, which may prolong the therapeutic effects of the drug. The half-lives of spironolactone and its metabolites are significantly increased in the setting of hepatic dysfunction and cirrhosis, with t1/2 of spironolactone increased to approximately 9 hours.[2] Additionally, dosing adjustments must be made in the setting of renal dysfunction or end stage renal disease, as spironolactone and its metabolites are primarily excreted via the urine, with secondary excretion in bile.[1]

Mechanism of Action

Spironolactone acts primarily through competitive inhibition of aldosterone receptors, and its main site of action is the blockade of the sodium potassium pump in the distal renal tubule.[1] The resulting increase in water and sodium excretion is largely responsible for the diuretic and antihypertensive effects that are beneficial in its approved indications. This inhibition also results in retention of potassium.[1] It also has direct inhibitory effects on the cardiovascular system's reactivity to the adrenergic and the renin-angiotensin-aldosterone systems.[4]

In addition, spironolactone produces anti-androgenic effects by targeting a variety of other mechanisms. Spironolactone has been shown to competitively inhibit binding of

5α-dihydrotestosterone (DHT) receptors in human prostate and human skin.[5] This binding likely plays a large role in its beneficial effects in dermatologic therapies and explains some of its potential side effects, such as decreased libido.

Animal studies have also shown spironolactone leads to destruction of cytochrome P-450 in the testicles and adrenal glands specifically, leading to a decrease in function of steroid hydroxylation. These effects lead to a decrease in both testicular testosterone formation as well as in plasma testosterone levels. Studies in humans have shown variable results in serum androgen levels. In women, spironolactone has been shown to decrease serum testosterone, while dehydroepiandosterone sulfate (DHEAS) levels either remain stable or decrease. Evaluation in males has shown either little or no decrease in serum testosterone levels. An increase in the clearance of testosterone has been demonstrated, shifting the ratio of testosterone to estrogen in favor of estrogen. This shift has been postulated to be the reason for the development of gynecomastia in males taking spironolactone.[5]

Aside from its effect on salt and water balance, the anti-androgenic effects of spironolactone account for its role in dermatology. Competitive inhibition of DHT in the skin as well as the variable effects on serum testosterone and DHEAS levels help modulate these hormones' effects in androgenic driven skin conditions, including acne, hirsutism, and androgenic alopecia.

Spironolactone in Dermatology

The off-label use of spironolactone in dermatology has been a growing area of therapeutics in the management of female cyclical acne and female pattern hair loss. The use of spironolactone as a first line agent for treatment of hirsutism and PCOS has been reviewed in the literature.[5,6,7] The appeal of utilizing spironolactone for these applications include its long-term safety, increasing data supporting efficacy, and relative lack of side effects, making spironolactone an attractive alternative to those failing traditional therapy or as a primary treatment.

Female Cyclical Acne

Although acne is typically thought of as a disorder of adolescents, there is a significant number of women that continue to struggle with acne into adulthood, and a large subset of women that present with new onset acne in their mid 20s and 30s. These patients classically present with worsening of their acne around menstruation, inflammatory papules and pustules, occasionally nodules or cysts on their lower face and neck, corresponding to the "beard area" in men. We typically describe this subset of patients as having "female cyclical acne" in our practice. These patients are therapeutically challenging as they typically present having failed multiple traditional treatments. In a study evaluating the features of post-adolescent acne in which 76% of the patients were women, 82% of the patients had failed to respond to multiple courses of antibiotics and as high as 32% relapsed after treatments with one or more courses of isotretinoin.[8]

The role of androgens and their effect on the sebaceous gland in increasing sebum production and causing follicular hyperkeratinization have been implicated in driving this subtype of acne, and therefore the therapeutic use of androgen receptor blocker medications such as spironolactone have been increasingly utilized in the treatment of hormonal acne. Studies have shown 30-50% reduction in sebum excretion with spironolactone administration.[9,10]The majority of women that present with female cyclical acne have normal systemic androgen levels; therefore the comedogenic effects of androgens are hypothesized to occur on the pilosebaceous units as a local imbalance of the androgen metabolism. Alternatively androgen receptor polymorphisms may cause local sensitivity to androgens, as well as abnormal post binding responses.[11,12]

In the literature there have been two randomized control trials and several uncontrolled studies reporting the efficacy of spironolactone in the treatment of acne in women, with all studies showing 50-100% improvement in acne. In the a recent retrospective review of the evaluation of the therapeutic effect of spironolactone in acne, efficacy was seen even in lower doses (50-100mg/day) with complete clearance or marked improvement in 66% of patients.[10,13,14,15,16,17] Studies have shown that clinical response can take up to 3 months, which is similar to other hormonal treatments.[18]

Adverse Effects

Common Side Effects

Spironolactone is generally well tolerated in the lower doses prescribed in dermatology (50-100 mg daily). Reported side effects include breast tenderness, urinary frequency, menstrual irregularities, hyperkalemia, fatigue, headache, dizziness, lethargy, hypotension, and birth defects. Menstrual irregularities may be minimized with the use of concomitant oral contraceptive pills. Mid-cycle spotting is among the most common irregularities.[19] The most dreaded side effect is hyperkalemia, which in most healthy patients, is clinically insignificant.[20,21] Approximately 13.7% of patients will experience detectable increases in their serum potassium levels.[22]

Other reported serious adverse effects include spironolactone-induced hepatitis.[23] In addition, DRESS syndrome from spironolactone has also been reported.[24] As mentioned earlier, gynecomastia has been reported in patients undergoing treatment for acne with spironolactone, developing within the first few months of treatment.[21,25,26]

Malignancy Potential

Although theoretically possible, estrogen-dependent malignancies have not been substantiated. Rodents given 25-250 times the usual human dose developed proliferative tumors such as benign thyroid and testicular adenomas, and malignant breast

tumors.[26] No cases of breast cancer linked to the use of spironolactone have been reported.[27] However, caution should be used when prescribing the medication to women with a personal or family history of breast cancer.[21,26]

Drug Interactions

Drug interactions with spironolactone center around its actions on its P-glycoprotein inhibition properties and its actions on the kidney as a potassium sparing/sodium wasting diuretic. As a P-glycoprotein modulator, it alters serum concentrations of medications that rely on these proteins for bioavailability such as digoxin.[28] Any drug that has a tendency to increase serum potassium such as heparin or trimethoprim, potassium containing medications such as penicillin G, or repeated transfusions with blood products containing potassium salts have been cautioned for use when on spironolactone.[29] In addition, medications that are dosed based on serum electrolytes can reach toxic levels, such as lithium, due to increased excretion of sodium. Medications that depend on the serum concentration of potassium, such as warfarin, may be altered when co-administered with spironolactone. When taken with other anti-hypertensives, spironolactone may cause hypotension. Caution must be taken when prescribing spironolactone to patients with renal insufficiency.

Dosing

Initially, recommendations for spironolactone dosing for acne were similar to the higher doses recommended for hair loss and hirsutism at 150- 200 mg/day.[30] Current data suggests that doses of 50mg-100mg/day result in significant improvement comparable to results seen in higher doses; in a recent study, 66% of patients dosed at 50-100mg/day of spironolactone showed marked improvement to complete resolution of acne lesions when compared to the previous studies of higher doses.[16] Anti-androgen activity may be augmented without increasing the dose of spironolactone by adding Ethinyl estradiol/drospirenone (EE/DRSP). Drospirenone is a derivative of 17 alpha spironolactone, which acts as an antagonist at androgen and aldosterone sites. The equivalent to approximately 20-25mg of spironolactone is 3mg of drospirenone.[20,31]

Drug Monitoring

Spironolactone does not appear to cause clinically significant elevations in serum potassium levels in healthy patients at acne doses (50-100mg). A study of 35 patients dosed at 100mg/day were monitored for 3 months, serum potassium levels showed no significant deviation from normal range during treatment.[32] A recent study evaluating low dose spironolactone (50-100mg) monitored potassium levels in 73 patients, and 13.7% showed mild hyperkalemia ranging from 4.8-5.3; however, these mild elevations were not considered to be clinically significant.[16] A study evaluating serum potassium levels in patients on spironolactone and EE/DRSP showed post therapy levels to be on average 4.35 with a range of 3.5-5.3.[20]

DISCUSSION

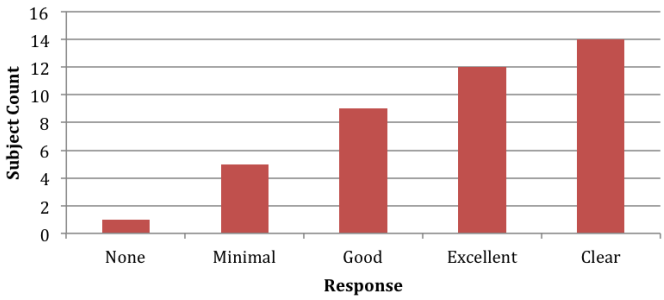
We conducted a retrospective chart review on 41 female adult patients with cyclical acne. Data was collected on 58 patients, however 17 were lost to follow up. The 41 female patients in this study were age 19-57. They were examined over the course of 2 to 102 months while taking 50 to 200mg of spironolactone and topical tretinoin 0.025% cream or adapalene 0.1% cream. The majority of patients had been on their topical retinoid prior to initiation of spironolactone treatment. All patients were prescribed 50-100mg of spironolactone with one patient with acne and alopecia on 200mg daily. All were diagnosed with acne rated mild to severe, prior to treatment, and were started on an initial dose of 50mg po daily. If significant improvement was not seen within the first 3-6 months, the dose was either held or increased in 25mg increments every 3 months. Eleven patients were increased to 75mg, and four patients were increased from 75mg to 100mg. The majority of patients were concurrently treated with tretinoin 0.025% or adapalene 0.1% cream and instructed to apply a thin layer to the face at bedtime. Patients on oral and topical antibiotics, as well as patients on photodynamic therapy were excluded from our study. The response to treatment was rated on a 0-4 scale with 0 being no response and 4 corresponding to clear skin. As shown in graph 1, only one patient (2.4%) had no response to treatment. This patient was only on 50mg po daily and only treated for 2 months. Only 5 (12.2%) patients had minimal response to treatment and 9 (22.0%), 12 (29.3%), and 14 (34.1%) had a good, excellent or clear response respectively. The study showed that 26 (63.4%) of women on treatment with spironolactone and topical retinoids had an excellent or clear outcome, and 35 (85.4%) were considered to have a good, excellent, or clear response. As the majority of patients in our study had been on retinoids prior to the initiation of spironolactone with minimal response, the addition of spironolactone to topical retinoid treatment suggests a superior response to retinoids alone in clearance of female adult cyclical acne.

In our review, there were minimal side effects noted as a result of spironolactone therapy. There was no change in tolerance to topical retinoids in any of the patients as a result of spironolactone treatment. Lightheadedness was reported in one patient (2.4%) on a 50 mg dose that subsided with continuation of treatment. Irregular periods were reported in two patients (4.9%), which occurred with dosages of 200 mg and 50 mg. Orthostatic hypotension was recorded in one patient (2.4%) taking a 50 mg dose. Only one flare (2.4%) was reported in a patient taking 50 mg. There were no severe adverse events in the women on treatment. None of our patients were elderly or had cardiac or renal abnormalities warranting electively following laboratory studies. There were no reports of malignancy in the patients taking spironolactone. This coincides with the lack of reported human malignancy cases to the FDA in the over 50 years spironolactone has been approved for medical use.

CONCLUSION

This study illustrates the significant benefits of using spironolactone and topical retinoids in female adult patients with cyclical acne. Many of the women in this study had been on chronic oral antibiotics for years with minimal improvement in their acne. Our experience shows spironolactone and topical retinoids provide an alternative and superior treatment strategy for the women in this cohort other than chronic oral antibiotics. Patients may be started on a 50mg po daily dose of spironolactone with nightly application of tretinoin 0.025% or adapalene and followed up within 3 months. If at this time there is minimal improvement, the dose can be increased to 75mg po daily and subsequently 100mg po daily if improvement is not seen over the course of 6-9 months time. We recommend follow up visits every 3 months for the first 9-12 months to establish a baseline dose and monitor for adverse effects. We establish prior to initiating therapy with spironolactone that there is no history of renal disease, concurrent potassium supplementation, or potassium sparing diuretic use. We did not routinely monitor potassium levels in this study or suggest dietary modification, as the data in the literature suggests minimal risk of hyperkalemia in low doses of spironolactone administered to young healthy patients with normal renal function. However, we recommend monitoring of baseline renal function and potassium levels every three months in patients with a history of cardiac disease or renal insufficiency, patients taking concurrent oral contraceptives with drospirenone and other potassium sparing diuretics, potassium supplementation, and ACE inhibitors. In addition, it may be prudent to monitor potassium levels in patients on higher dosages of spironolactone (150mg-200mg) every 3 months. To help clarify the risks of spironolactone, we encourage studies with larger sample sizes, longer length of follow up, and carefully conducted medical histories concerning newly diagnosed malignancies in patients on spironolactone. Our experience shows spironolactone is a safe and important drug in treating women with adult cyclical acne along with topical retinoids.

FIGURE 1. Acne Response to Spironolactone and Topical Retinoids.



DISCLOSURES

None of the authors have any relevant conflicts to disclose.

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