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EDITORIAL

K+larity for Spironolactone At Last!

Emmy M. Graber, MD, MBA

Spironolactone was approved by the US Food and Drug Administration (FDA) 30 years ago for several noncutaneous conditions, such as congestive heart failure. It acts as an aldosterone antagonist and thereby promotes diuresis, reduces blood pressure, and retains potassium.[1] Aside from these mechanisms of action, spironolactone also exerts several antiandrogenic effects in the skin. Spironolactone decreases sebum production by competing with both dihydrotestosterone (DHT) and testosterone for the androgen receptors and also halts the conversion of testosterone to the more potent sebum producer DHT. In addition, spironolactone decreases type 2 17β-hydroxysteroid dehydrogenase and thereby inhibits its androgen synthesis.[2] These antiandrogenic actions make spironolactone well suited to treat androgen-driven cutaneous disorders, such as acne.

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Although spironolactone is not FDA approved to treat acne, there are many of us who regularly prescribe spironolactone for acne with great success. Adult female acne, which is hormonally driven, is particularly pronounced on the lower face, jawline, and neck. Such hormonal acne is often described as flaring in a cyclical nature—either just before or just after menses. For patients who may fit into this clinical picture, spironolactone can be especially useful.

Studies evaluating the efficacy for spironolactone are sparse, but those that exist are compelling. One prospective study[3] of 64 women prescribed spironolactone found that in all, acne improved to some degree and over half of them were clear after spironolactone use. Another smaller study[4] followed 27 women with severe acne and found that 85% were entirely clear or had "excellent" results (>75% clearance) at 6 months. Because of the paucity of data, the efficacy of spironolactone for acne treatment is considered indeterminate by the Cochrane Database.[5]

Because some studies suggest superb results with spironolactone, and with the push to limit oral antibiotic use, why would dermatologists not prescribe spironolactone for adult hormonal acne? I suspect that many physicians balk at giving spironolactone owing to fear of adverse effects. The potential adverse effects include breast tenderness, menstrual irregularities, hypotension, and the oft-feared hyperkalemia. Concomitant oral contraceptive use can offset any breast tenderness and menstrual irregularities. Hypotension is rare and minimal—only an average 5% drop in blood pressure may be noted in otherwise healthy individuals.[6] Hyperkalemia from any etiology, when severe enough, can cause cardiac arrhythmias and death.

Wait...What? Cardiac arrhythmias and death? Is spironolactone prescribing not for the faint at heart? Is this fear of hyperkalemia with spironolactone use founded on evidence, or is this concern unjustified?

Prior to the report by Plovanich et al[7] in this issue of *JAMA Dermatology*, only a few studies supported the safety of spironolactone in otherwise healthy patients. Shaw et al[6] found a clinically insignificant increase in potassium in 10% of 85 patients. In another study, no hyperkalemia was seen in 35 patients, all of whom were prescribed spironolactone at a dosage 100 mg per day.[8]

Many patients prescribed spironolactone concomitantly take an oral contraceptive pill. The newer generation of oral contraceptives containing the progestin drospirenone may theoretically increase the risk of hyperkalemia because they are also aldosterone antagonists. A study[4] looking at 27 patients prescribed both spironolactone and drospirenone-containing oral contraceptives found no cases of hyperkalemia. Despite the intriguing results of this study[4] and others, their small sample size undermines the findings.

Finally, Plovanich et al[7] provide us with a large, well-designed study to assuage our fears of hyperkalemia. Their results showing no increased risk of hyperkalemia in patients with acne prescribed spironolactone will surely change the way many clinicians practice. However, it should be noted that the patients with acne in their study[7] included only "young healthy females," and those with cardiac disease, renal disease, or prescribed medications potentiating the risk of hyperkalemia were excluded. While the physician may feel reassured that he or she does not need to check potassium levels in otherwise healthy individuals, one should do a thorough review of a patient's medications and medical history to ensure safety with spironolactone use.

Still, some dermatologists may not feel comfortable prescribing spironolactone despite the now-palliated fears of hyperkalemia. What about spironolactone's potential to cause feminization of male fetus genitalia, and what about the black box warning on spironolactone? In a study[9] in which pregnant rats were treated with 5 times the human dose of spironolactone, male offspring showed evidence of genital feminization, yet no human studies support this risk. MicroMedex,[10] a collection of different drug databases, finds the "magnitude of teratogenic risk to a child born after spironolactone exposure during gestation to be undetermined." MicroMedex does comment that the quality and quantity of data on which this risk estimate is based is "very limited." In regard to the black box warning, the manufacturer recommends avoiding

"unnecessary use" as spironolactone has been shown to induce endocrine tumors in rats.[11] However, such studies may not be comparable with human use. Rats given spironolactone for 2 years at 10 to 500 times the human dose showed increased risk of tumors (although many were benign adenomas) of the breast, liver, and myeloid leukocytes.[12] Although extrapolated from exorbitantly high dosages in rats, these results led manufacturers to include a black box warning recommending avoidance of long-term spironolactone use. Despite suggestions that there may be an increased risk of some endocrine tumors, there exists no association between spironolactone use and breast cancer.[13]

As supported by the findings in this study,[7] there is great intervariability among physicians' frequency of potassium monitoring. Studies such as this one are important in that they standardize care and thereby reduce unnecessary spending. More frequently, employers and third-party insurers are relying on the "value" of a clinician's care to determine reimbursement. Our value is calculated by care quality divided by cost. If our costs increase, the value of our care is lessened. This has important implications because the strength of our specialty will be diminished if we are deemed less valuable.[14]

Fears of adverse effects of medication amplify like an urban legend among prescribers. Because of studies like that of Plovanich et al,[7] we can elucidate fact from fiction and better serve our patients while calming our own fears. Furthermore, understanding the safety of medications prevents unnecessary laboratory monitoring and results in drastic cost savings. The authors should be commended for providing clarity about spironolactone monitoring and thereby improving our patient care.

ARTICLE INFORMATION

Author Affiliation: Department of Dermatology, Boston University, Boston, Massachusetts.

Corresponding Author: Emmy M. Graber, MD, MBA, Department of Dermatology, Boston University, 609 Albany St, J-107, Boston, MA 02118 (621.emmy@gmail.com).

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REFERENCES

1. Shaw JC. Spironolactone in dermatologic therapy. *J Am Acad Dermatol*. 1991;24(2, pt 1):236-243.

2. Clarke SB, Nelson AM, George RE, Thiboutot DM. Pharmacologic modulation of sebaceous gland activity: mechanisms and clinical applications. *Dermatol Clin*. 2007;25(2):137-146.

3. Sato K, Matsumoto D, Iizuka F, et al. Anti-androgenic therapy using oral spironolactone for acne vulgaris in Asians. *Aesthetic Plast Surg*. 2006;30(6):689-694.

4. Krunic A, Ciurea A, Scheman A. Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone. *J Am Acad Dermatol*. 2008;58(1):60-62.

5. Brown J, Farquhar C, Lee O, Toomath R, Jepson RG. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database Syst Rev*. 2009;(2):CD000194.

6. Shaw JC. Low-dose adjunctive spironolactone in the treatment of acne in women: a retrospective analysis of 85 consecutively treated patients. *J Am Acad Dermatol*. 2000;43(3):498-502.

7. Plovanich M, Weng QY, Mostaghimi A. Low usefulness of potassium monitoring among healthy young women taking spironolactone for acne [published online March 23, 2015]. *JAMA Dermatol*. doi:10.1001/jamadermatol.2015.34.

8. Yemisci A, Gorgulu A, Piskin S. Effects and side effects of spironolactone therapy in women with acne. *J Eur Acad Dermatol Venereol*. 2005;19:163-166.

9. Hecker A, Hasan SH, Neumann F. Disturbances in sexual differentiation of rat foetuses following spironolactone treatment. *Acta Endocrinol (Copenh)*. 1980;95(4):540-545.

10. Truven Health Analytics Inc. MicroMedex website. http://www.micromedexsolutions.com/home/dispatch. Accessed February 23, 2015.

11. Aldactone (spironolactone) black box warning. https://online.epocrates.com/u/10b2181/Aldactone/Black+Box+Warnings. Accessed February 23, 2015.

12. Bergstrom KG. Everything old is new again: spironolactone and metformin in the treatment of acne. *J Drugs Dermatol*. 2010;9(5):569-571.

13. Danielson DA, Jick H, Hunter JR, Stergachis A, Madsen S. Nonestrogenic drugs and breast cancer. *Am J Epidemiol*. 1982;116(2):329-332.

14. Graber EM, Burns LR. The value of our care. *JAMA Dermatol*. 2014;150(9):935-936.