Prescribing Spironolactone Safely & Potential Side Effects

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This Entire Talk Is Off Label
What Are Physicians Worried About

• “Is anyone still checking potassium when giving Spiro? I don’t usually prescribe more than 100mg/qd. What if also taking drospirenone containing OCPs?”

• “I check potassium anyway for peace of mind”

• “I check urine pregnancy test and BP at initial visit, then 2 months later sodium, potassium and BP. Kind of overkill”

• “Check BP at every visit”

• “Check BP at every visit and K+ if on ACE or ARB”
What Are Physicians Worried About

- “I reduce my Spiro dose if they are on drosperinone containing OCPs since it is equivalent to 25mg of Spiro”
- “Patients must be on OCPs or IUD or unable to get pregnant”
- “I worry about the interaction of Spiro with certain antidepressants, as supposedly the combo can cause SIADH”
- “Increased risk of blood clots with Spiro and OCPs”
- “What about tumor risk?”
Overview

• Hormonal Therapy
• Uses and Contraindications for Spironolactone
• Safety Data on Spironolactone
• How I Prescribe Spironolactone
Hormonal Therapy

• ½ women in 20s, 1/3 in 30s and ¼ in 40s has acne

• 63% of women have a premenstrual increase in number of inflammatory lesions
  – OCPs and spironolactone can dramatically decrease

• Routine screening usually reveals normal hormone levels
  – Are sebaceous glands more sensitive
  – Is there more local/skin production of hormones affecting sebaceous glands

Hormonal Therapy

• Ovaries and adrenal glands are main source of androgen production

• Testosterone and DHT are main androgens affecting acne
  – Androgen receptors expressed on basal layer of seb glands and outer root sheath of hair follicle

• In sebaceous glands:
  – DHEA → Androstenedione → Testosterone → DHT in cells (via 5α-reductase type 1) → transcription of androgen response genes

Hormonal Therapy

• Even important if all hormone levels are normal
• GOAL: Oppose effects of androgens on seb glands
• Alternative to repeat isotretinoin or po antibiotics
• 4 main groups:
  – Androgen receptor blocker (ie Spironolactone “antiandrogen”)
  – Adrenal androgen production blocker (glucocorticoids)
  – Ovarian androgen blockers (OCPs)
  – Enzyme inhibitors (Dutasteride)
Spironolactone

- Androgen receptor blocker
- Primary active metabolite is canrenone → aldosterone antagonist, antiandrogenic and diuretic
- Not FDA approved for acne/dermatologic conditions (HTN, CHF 30 yrs) - Off label
- Used for acne and hirsutism 20+ years
- MOA: competes with testosterone and DHT for androgen receptors and decreases androgen stimulated sebum production
Mechanism of Action

• Decreases 5-alpha reductase activity via increased clearance of testosterone

• Increases steroid hormone binding globulin (SHBG) → reduces circulating free testosterone → gynecomastia or decreased libido

• Compete locally with dihydrotestosterone (DHT) for cutaneous androgen receptors → inhibiting testosterone and DHT binding
  – Ability to inhibit androgens at different levels has led to its use in women with androgenic alopecia, hirsutism, and excess sebum production
FDA Approved Uses

• Primary Hyperaldosteronism (Adrenal tumor)
• CHF
• Cirrhosis with Edema/Ascites
• Nephrotic Syndrome
• Hypertension
• Hypokalemia
Contraindications

- Renal Insufficiency
- Anuria
- Hyperkalemia
- Pregnancy - Pregnancy Category C
- Estrogen-dependent malignancy - familial or personal
- Abnormal Uterine Bleeding
Pharmacokinetics

• Peak levels in blood 2-4 hours
• >90% bioavailable, food increases absorption
• Half-life 10-35 hours (12.5 spiro, 19.2 canrenone)
• Canrenone is the active metabolite/aldosterone antagonist
• Metabolized in liver, excreted in urine
Spironolactone Drug Interactions

- Reduced diuretic effect with salicylates
- ACE inhibitors increase risk of hyperkalemia
- Potassium supplements increase risk of hyperkalemia
- Can increase blood Digoxin levels → toxicity
Spironolactone Efficacy

• Low-dose adjunctive spironolactone in the treatment of acne in women: A retrospective analysis of 85 consecutively treated patients. Shaw JAAD 2000
  – Records reviewed from 85 women with acne treated with spironolactone 50 to 100 mg/day (LOW DOSE)
    • Monotherapy or as an adjunct to standard therapies
    • The maximum length of treatment was 24 months
  – 33% had clearing of acne, 33% had marked improvement, 27.4% showed partial improvement, and 7% showed no improvement
  – The treatment regimen well tolerated
    • 57.5% no adverse effects
Spironolactone Dosing

• Available in 25mg, 50mg, 100mg tablets

• Dose: 25-100 mg QD-BID
  – Can take 3 months to work although results by 4-8 weeks (first menses will have smaller cysts that resolve more quickly)

• Higher doses often less tolerated
What Are We Worried About?

• Most worrisome side effects:
  – Hyperkalemia (new onset muscle cramps or weakness)
  – Hyperkalemia may cause fatal cardiac irregularities, paresthesia, muscle weakness, fatigue, flaccid paralysis of the extremities, bradycardia, and shock

• Pregnancy avoidance due to feminization of male fetus and hypospadias
  – Therefore important to use with birth control
  – Sign consent form if not on birth control

• Early concerns about risk of breast ca have not been supported
Spironolactone Safety

  - Survey questionnaire sent to 210 patients
  - 91 women (18-52 y/o) with acne followed for 8 years
  - 506 patient-years of f/up and 200 person-years spironolactone exposure
  - 50-100mg po qd
  - Mean treatment length 28.5 months (0.5-122 mo)
Spironolactone Safety

• Long-Term Safety of Spironolactone in Acne: Results of an 8-Year Followup Study. Shaw J et al 2002 J Cutan Med Surg
  – No cases of serious illnesses attributed to Spiroronolactone
  – 59% had side effects, 15% lead to discontinuation
  – Most common: Diuretic effect (29%) and menstrual irregularities (22% with mid cycle spotting 15%)
  – Breast tenderness (17%), decreased libido (15%)
  – Fatigue (17%), H/A (14%), dizziness (12%), lightheaded (11%)
Spironolactone Safety

- 15% (67 women) stopped Spironolactone
- Reasons for Cessation: 15% side effects, 29% treatment failure, 21% concern about long term side effects, 19% no longer needed, 6 desired pregnancy
Spironolactone Safety

• Long-Term Safety of Spironolactone in Acne: Results of an 8-Year Followup Study. Shaw J et al 2002 J Cutan Med Surg

• Long term safety assessed in 84 patients
  • 7 had abnormal mammos- 4 had benign breast biopsies
  • No cases of breast carcinoma
  • 5 patients had ovarian cysts, 4 had abnormal pap smears

• **Long term use of Spironolactone for acne appears to be SAFE**
Spironolactone Side Effects

  - 54 patients taking spironolactone for hirsutism or acne
  - 91% of patients report side effects with 200mg daily
  - 80% have anti-androgenic SE (menstrual disturbances, breast enlargement and tenderness)
  - Concomitant use OCPs gave lower incidence of menstrual abnormalities
Spironolactone Side Effects

  – Only 13% had to stop the drug
    • 13% headaches, 20% dizziness
  – A reduction in dose improved side effects
  – Side effects tended to occur early → regular review during the initial 3 months of treatment is recommended
Spironolactone Side Effects

• Most frequent are typically dose-related
  – Diuresis (29%)
  – Menstrual irregularities (22%)
  – Breast tenderness (17%), breast enlargement, fatigue, headache, and dizziness

• Pregnancy category C: animal studies have shown feminization of a male fetus early in gestation
  – Concomitant use of OCP to both regulate menses and prevent unwanted pregnancy
Spironolactone Side Effects

• Menorrhagia/menstrual irregularities common at 100mg QD
  – Tend to improve after 2-3 months of therapy
  – Decreasing dose to 50-75mg can help
  – Add an OCP
  – Cycling the spironolactone (like OCPs) for 21 days on and 7 days off
Spironolactone and OCPs

- Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone. Shaw JAAD 2007
  - 27 women 18-43 y/o with either severe papular or nodulocystic facial acne treated with combined oral contraceptive containing 30 g ethinyl estradiol and 3 mg drospirenone (EE/DRSP; Yasmin) and spironolactone 100 mg QD
  - Serum potassium level obtained before initiation of therapy, then 4-6 weeks after the start of both medications
Spironolactone and OCPs

- Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone Shaw J JAAD 2007
  - No significant elevation of serum potassium was found
  - No side effects significant enough to discontinue treatment

- At follow up, 85% of subjects were entirely clear of acne lesions or had excellent improvement (75% improvement), 7.4% were mildly improved, and 7.4% were not improved
Using Spironolactone with OCPs

• Excellent monotherapy especially if intolerant of OCPs

• When used in combination with an OCP→ improving acne, decrease chance of pregnancy, improve side effects

• Women of childbearing potential must be on a reliable form of birth control

• Decrease potential menstrual side effects from Spiro
What Are Physicians Worried About?

• Most worrisome side effects:
  – Hyperkalemia (new onset muscle cramps or weakness)- Concern is in heart failure patients on other medications that interfere with K+ excretion
  – Hyperkalemia may cause fatal cardiac irregularities, paresthesia, muscle weakness, fatigue, flaccid paralysis of the extremities, bradycardia, and shock

• Feminization of male fetus and hypospadias
  – Therefore important to use with birth control
  – Sign consent form if not on birth control

• Early concerns about risk of breast ca have not been supported
Do We Need to Monitor Potassium?

- Low Usefulness of Potassium Monitoring Among Healthy Young Women Taking Spironolactone for Acne JAMA Derm Sept 2015 Plovanich et al
  - Large retrospective study 2000-2014 comparing rates of hyperkalemia in 974 healthy young females age 18-45 with acne or endocrine disorders with associated acne (PCOS)
  - Also examined rates of hyperkalemia in 1165 healthy young women for baseline rates
  - Results: 13 mildly elevated potassium levels in acne group (hyperkalemia rate 0.72%) which was equivalent to the comparison group
  - CHF, renal disease, HTN patients excluded. Drospirenone containing OCPs included
Do We Need to Monitor Potassium?

• Study concludes that it is unnecessary to routinely monitor potassium in healthy young women (<45)

• BUT...in NYC, everyone drinks coconut water, eats bags of kale chips and loves bananas...

• Therefore, check medical history and medications carefully on all patients

• New onset muscle cramps, weakness, palpitations should trigger potassium check

• For those 45+, check before and after 1 month or after increasing dose
Spironolactone and Potassium

• Serum potassium monitoring should be considered in:
  – Patients >45 years old
  – Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal antiinflammatory drugs, and digoxin

• Measurements performed at baseline, 4 weeks after initiation, and after dose increases

• Educated patients about avoiding foods that are high in dietary potassium, such as low-sodium processed foods and coconut water
Potassium Rich Foods

• 1) Avocado. 1 whole: 1068 mg (30% DV)
• 2) Spinach. 1 cup: 839mg (24% DV) or Kale (491mg (14% DV)
• 3) Sweet potato. 1 medium: 952 mg (27% DV)
• 4) Coconut Water. 1 cup 600 mg (17% DV)
• 5) Yogurt. 1 cup: 579 mg (15% DV)
• 6) White Beans. ½ cup: 502 mg (15% DV)
• 7) Banana. 1 large: 422 mg (12% DV)
• 8) Acorn squash. 1 cup: 899 mg (26% DV)
• 9) Dried Apricots. ½ cup: 755 mg (22% DV)
• 10) Mushroom. 1 cup: 428 mg (27% DV)
Spironolactone and Cancer

- **BLACK BOX WARNING:** Animal studies using 25-250 times human doses of spironolactone developed thyroid, hepatic, testicular, and breast adenomas, as well as thyroid carcinoma and myelocytic leukemia.

- Only 1 human report suggesting carcinogenicity identified 5 hospitalized patients with breast cancer who were taking spironolactone among other medications.
Spironolactone and Breast Cancer

- BMJ 2012 Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study (Mackenzie et al)
  - Exposed cohort 28,032 and control cohort 55,961 1987-2000
  - Incidence rates between 2 groups the same: 0.39 vs 0.38% per year
  - Women >55 y/o on spironolactone for CVD (no prior breast ca history)
  - Conclusion: NO INCREASED RISK OF BREAST CANCER IN THOSE EXPOSED TO SPIRONOLACTONE
Spironolactone and GYN cancers

- Spironolactone use and the risk of breast and gynecologic cancers 2013 Cancer Epidemiol. Biggar et al

  - Large retrospective cohort study of 2.3 million women representing 28.8 million person-years that showed no association between spironolactone use and the development of breast, uterine, cervical, or ovarian cancers
Spironolactone and Embryogenesis

• Disturbances in sexual differentiation of rat foetuses following spironolactone treatment Acta Endocrinol Dec 1980 95 540-545
  – Pregnant rats treated with 40 mg spironolactone late embryogenesis and fetal development
  – Male fetuses showed feminization of external genitalia
  – Anogenital distance was 48% shorter than that of the controls
  – Number and size of prostatic buds were significantly reduced
  – No studies in humans
Spironolactone and Embryogenesis

- Risk of feminization of the male fetus occurs 6 weeks post-conception in humans.
- Potential risk to the male fetus is negligible if Spironolactone discontinued early.
- Preg Cat C and avoid in pregnancy due to this risk.
- Avoid in men given impotence, gynecomastia, and loss of libido.
Spironolactone and Lactation

- Unclear if Spironolactone is excreted in human breast milk
- Canrenone (active and predominant metabolite) does achieve levels in human breast milk
- Max exposure of the breast-fed infant to canrenone is 0.2 percent of the maternal daily dose → Insignificant
- American Academy of Pediatrics classifies spironolactone as compatible with breastfeeding
Spironolactone and Isotretinoin

- No studies addressing this but personal experience is that these are safe together and work well for adult female acne
Spironolactone and Antibiotics

• The efficacy and safety of amoxicillin, trimethoprim-sulfamethoxazole, and spironolactone for treatment-resistant acne vulgaris. Turowski CB, James WD Adv Dermatol. 2007; 23():155-63.
  – Safety demonstrated with with TCN, Mino, amoxicillin

  – Hyperkalemia has been reported to occur with high doses of TMP-SMX in human immunodeficiency virus (HIV)-infected patients, the elderly, and patients with renal insufficiency
Spironolactone: How I Use It

• Start 50-100mg po qd
  – Increase to 150-200 if needed - BID dosing helpful
  – Reevaluate patients month 1, 3 then every 6 months if stable

• Check serum potassium beforehand, after 1 month and after any further increase if 45
  – Give 1 month supply only
  – Bananas, kale, coconut water in moderation

• Do not monitor blood pressure (unless over 225mg)

• Sign consent form if not on birth control
Conclusions

• Spironolactone is safe and effective – No need to monitor Potassium, BP

• Hormonal therapy should be considered 1st line for adult female acne

• Most frequent side effects: Diuresis (29%), Breast tenderness (17%), Menstrual irregularity (22%)
  – Can be alleviated by lowering the dose and concomitant OCPs

• Avoid pregnancy (Pregnancy Category C)
  – Feminization of male fetus
    • Concomitant use of OCPs beneficial