Conflict of Interest Disclosure

- none
Spironolactone

- FDA-approval in 1960

- Current FDA-approved indications:
  - Primary hyperaldosteronism
  - Edematous conditions for patients with CHF
  - Cirrhosis of the liver
  - Nephrotic syndrome
  - Essential hypertension
  - hypokalemia

Spironolactone is not FDA-approved for acne
Spironolactone

- Aldosterone antagonist => diuresis and lowering of blood pressure
- Anti-androgen => improvement in acne and hirsutism
  - Androgen receptor blocker
  - Decreases androgen production
  - Inhibits 5α-reductase
  - Increase SHBG
Efficacy
Spironolactone- efficacy

- RCT in 21 women showed that spironolactone, 200mg daily, significantly improved acne as assessed by subjective benefit, number of inflamed lesions and by an independently evaluated photographic method.


- Retrospective chart review of 85 consecutive women treated with spironolactone 50-100mg daily either as monotherapy or as an adjunct to standard therapy.
  - 33% cleared
  - 33% marked improvement
  - 27.4% partial improvement
  - 7% no improvement

  *Shaw J.  JAAD 2000;43:498-502. S*
Spironolactone

- Cochrane database review conclusion:
  - There is insufficient data to support efficacy of spironolactone in the treatment of acne.

139 Japanese patients with acne (116 females, 23 males) started on 200mg daily of spironolactone

20 weeks of treatment
- 200mg daily for first 8 weeks
- After initial 8 weeks, dose lowered by 50mg every 4 weeks
- 64 females completed the 20 week study
- Gynecomastia developed in 3 males within 4-8 weeks and subsequently treatment was discontinued in all males

52 of 116 females dropped out of study for various reasons including menstrual irregularities although most patients who completed the regimen also experienced menstrual irregularities (80% of 116)

All 64 females who completed the 20 week regimen exhibited clinical improvement

- 53% excellent
- 47% good

Fig. 2. A 27-year-old female with acne vulgaris from the jawline to the neck who did not improve with repeated alpha hydroxy acid (AHA) peeling and oral antibiotics. (A) Before treatment. (B) After 20 weeks of oral spironolactone (excellent results, fewer inflammatory spots).

Fig. 3. A 31-year-old female with acne vulgaris and seborrheic dermatitis on the whole face. (A) Before treatment. (B) After 4 months of oral spironolactone (excellent results). Sebum discharge was markedly reduced, and seborrheic dermatitis and acne both improved.
Fig. 4. A 28-year-old female with acne vulgaris and severe sebum discharge. (A) Before treatment. (B) After 4 months of oral spironolactone (excellent results).
Side effects
Spironolactone- side effects

- Side effects are dose-related:
  - diuresis (29%)
  - menstrual irregularities (22%)
  - breast tenderness (17%)
  - breast enlargement
  - fatigue
  - headache
  - dizziness

- **Pregnancy category C:** Concomitant use of COC is recommended to both regulate menses and to prevent pregnancy in many patients

Spironolactone is not FDA-approved for the treatment of acne

Spironolactone and K+

- N=85 (on spironolactone alone or in combination with ocp or antibiotic)
- 50-100mg of spironolactone
- 73 evaluable subjects
- Mild, clinically insignificant hyperkalemia (4.8-5.3mEq/L) in 10 (13.7%)


Spironolactone is not FDA-approved for the treatment of acne
Japanese study of 139 acne patients treated with spironolactone
- 200mg daily for first 8 weeks
- After initial 8 weeks, dose tapered by 50 mg every 4 weeks

64 female subjects completed the regimen

No significant changes in K+

Spironolactone and K+

- 27 women with acne treated with both a COC containing 30μg of ethinyl estradiol and 3 mg drospirenone and spironolactone 100mg daily

- Serum K+ was obtained before initiation of therapy and 4-6 weeks after the start of both medications

- No significant elevation of serum K+ was found in any subject

Krunic et al. JAAD 2008;58:60-2.
Spironolactone and K+

- Retrospective study of 974 healthy young women taking spironolactone for acne vs 1165 healthy young women taking and not taking spironolactone

- 18-45 years of age with no cardiovascular disease, renal failure, or use of medications that affect the renin-angiotensin-aldosterone system

Plovanich M et al. JAMA Dermatology online March 22, 2015.
RESULTS:

There were 13 abnormal serum potassium measurements in 1,802 measurements obtained among young women receiving spironolactone therapy for acne (hyperkalemia rate = 0.72%). Baseline rate of hyperkalemia in this population is 0.76%.

CONCLUSION:

Routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne.

Plovanich M et al. JAMA Dermatology online March 22, 2015.
Spironolactone and K+

Check K+ if:

- Older age
- Hx of renal or cardiac disease
- Hx of impaired hepatic function (minor alterations of fluid and electrolyte balance may precipitate hepatic coma)
- Higher doses of spironolactone (200mg/day)

Spironolactone is not FDA-approved for the treatment of acne
Spironolactone and K+

- Check K+ if on certain medications:
  - ACE inhibitors
  - Angiotensin II antagonists
  - Aldosterone blockers
  - NSAIDS (i.e. indomethacin)
  - Salt substitutes
  - K+ supplementation
  - Trimethoprim/sulfamethoxazole
Sprironolacatone and K+

- Trimethoprim decreases urinary K+ excretion by 40%
- Population-based, nested case-control study of Ontario residents aged 66 or older treated with spironolactone between 1992-2010
  - 165,754 treated with spironolactone
  - 17,859 (10%) received at least one prescription for TMP-SMX
  - TMP-SMX was associated with a marked increase in the risk of hospital admission for hyperkalemia

Spironolactone and K+

- Conclusion:
  - 60% of all cases of hyperkalemia in older patients taking spironolactone and treated with an antibiotic for UTI could be avoided if TMP-SMX was not prescribed.

Antoniou et al. BMJ 2011;343:d5228

- Interpretation: TMP-SMX was associated with an increased risk of sudden death among older patients taking spironolactone. When clinically appropriate, alternative antibiotics should be considered.
Hyperkalemia - warning signs

- Parasthesia
- Muscle weakness
- Fatigue
- Flaccid paralysis of extremities
- Bradycardia
Spironolactone and other drugs

- **Lithium**
  - Diuretics reduce the renal clearance of lithium and should not be used with lithium

- **Digoxin**
  - Spironolactone increased the half life of digoxin and increases the risk of toxicity
Spironolactone and breast cancer

- FDA Black Box Warning:

  *Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Spironolactone should be used only in those conditions described under Indications and Usage. Unnecessary use of this drug should be avoided.*

(Dosages used in these rat studies were 25-100 times higher than those administered to humans; benign adenomas of the thyroid and testes, malignant mammary tumors, proliferative changes in the liver)


Spironolactone is not FDA-approved for the treatment of acne
Spironolactone and breast cancer

- N=1,475
- Prescribed spironolactone for 3-7 years
- 9 cases of breast cancer vs age-specific rate of 8.3 cases

- N=461 person-years
- 3 years of follow-up after exposure to spironolactone
- No relationship between spironolactone and breast cancer

- Five case-control studies have also found no overall increase in the relative risk for breast cancer associated with spironolactone


Spironolactone is not FDA-approved for the treatment of acne
Spironolactone use and the risk of breast and gynecologic cancers

- 2.3 million women >20 years of age followed for 28.8 million person-years using a Danish nationwide prescription drug registry
- 1.3 million spironolactone prescriptions between 1995-2010
- No evidence of increased risk of breast, uterus or ovarian cancer with spironolactone use.

Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study.

- 1,290,625 women older than 55 (8.4 million patient years)
- Exposed cohort included women who received at least 2 prescriptions of spironolactone after 55 years of age
- 2 unexposed matched controls per case
- 29,491 new cases of breast cancer were recorded in the study population
- No difference in breast cancer rates between exposed and nonexposed cohorts (hazard ratio 0.99, 95%CI 0.87-1.12)

Spironolactone and pregnancy/nursing

- Spironolactone is pregnancy category C
  - Spironolactone should NOT be used during pregnancy
  - Increased risk of hypospadias and feminization of the male fetus

- Spironolactone’s active metabolite canrenone has been found in breast milk but at 0.2% of the maternal dose. Both the AAP and the WHO classify spironolactone as compatible with lactation.

Murase et al. JAAD 2014;70:401.e1-14.
Butler et al. JAAD 2014;70:417.e1-10.
Practical approach
Spironolactone

- Dosages 25mg-200mg (I prefer a max dose of 100mg)

- Side effects:
  - menstrual irregularities
  - breast tenderness/swelling
  - fatigue
  - headaches

- Higher doses = higher rate of side effects

- Concomitant use of oral contraceptive lessens menstrual irregularities and prevents pregnancy (risk of feminization of male fetus in late first trimester)

Spironolactone is not FDA-approved for the treatment of acne
Spironolactone

- Food increases bioavailability by almost 100% (Package insert)
How quickly does it work?

- No good objective answer
  - Studies are small and frequently spironolactone is used as an adjunct to other topical or oral medications

- I counsel patients that it may take 3 months to see a meaningful response, similar to other hormonal based therapies
How long?

- Long term unless:
  - Side effects
  - Pregnancy
  - No longer needed

- Surveys of 91 women followed for 8 years (200 person years exposure to spironolactone; mean treatment length=28.5 months) found no serious illness thought to be attributed to spironolactone

Thank you
American Acne & Rosacea Society

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