POTASSIUM SPARING DIURETICS

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[Potassium Sparing Diuretics | Mechanism of Action, Indications, Adverse Reactions, Contraindications]

Medical Editor: Abigail S. Xu, RPh

OUTLINE

I) MECHANISM OF ACTION

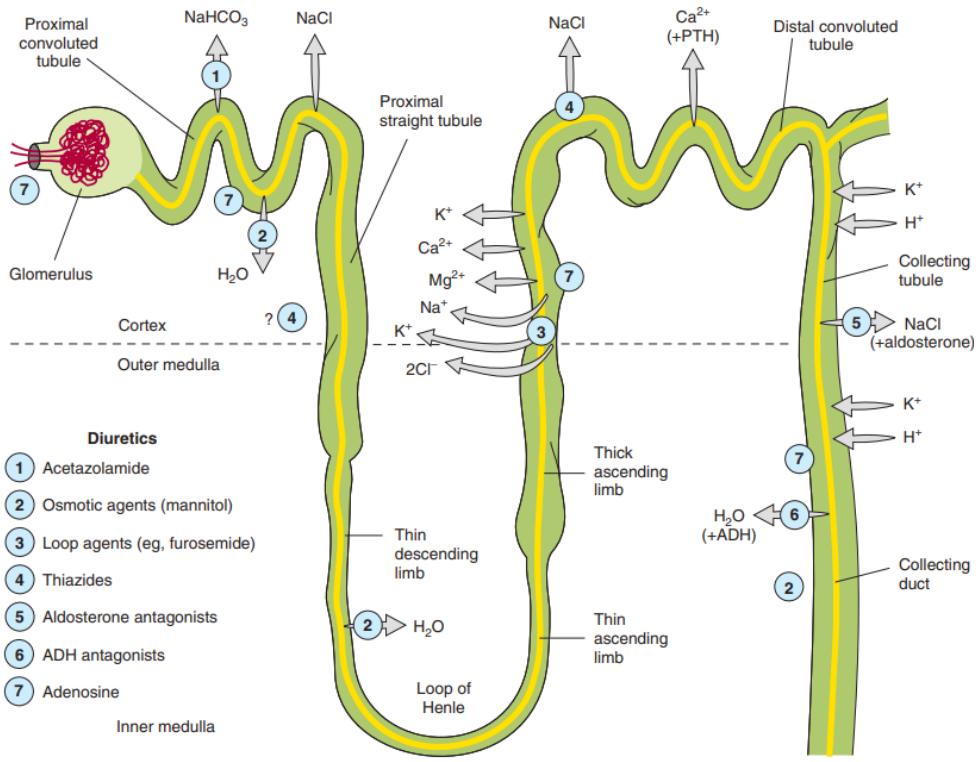

Figure 1. Renal Tubule Transport Systems and Sites of Action of Diuretics [Trevor, Katzung, & Kruidering-Hall, 2015, p. 133, Fig. 15-1]

(A) NORMAL PHYSIOLOGY

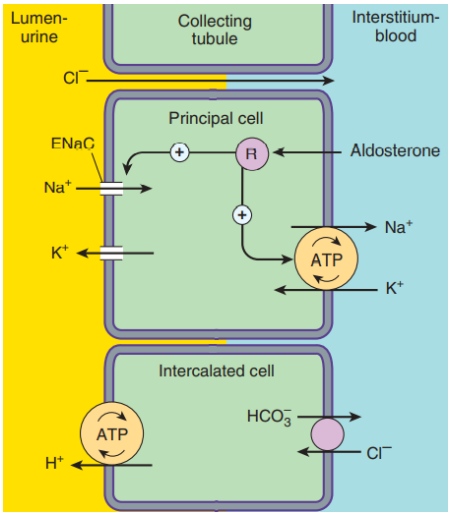

Figure 2. Mechanism of Na^+, K^+, and H^+ ion movement in the collecting duct [Trevor, Katzung, & Kruidering-Hall, 2015, p. 137, Fig. 15-5]

End of Distal Convoluted Tubule & Collecting Duct

- Responsible for **reabsorption of 2-5%** of total filtered **sodium** under normal circumstance; more if aldosterone is increased [Trevor, Katzung, & Kruidering-Hall, 2015]
- Dependent of the following **Hormones**
  - **Antidiuretic hormone (ADH)**
    - control **water balance**
  - **Aldosterone**
    - Controls **Na^+, Cl^-, K^+, and water** balance
- **Cell Types**
  - **Principal Cells**
    - Regulate electrolyte or ion balance
  - **α-Intercalated Cell**
    - acid-base balance

(B) ALDOSTERONE PHYSIOLOGY

- Secreted by the **zona glomerulosa** (top layer) of the adrenal cortex

Recall: Adrenal Cortex Physiology

Table 1. Layers of the Adrenal Cortex and Hormones Secreted

Zones	Hormones
Zona Glomerulosa (top)	Aldosterone
Zona Fasciculata (middle)	Cortisol
Zona Reticularis (inner)	Androgens

Stimulants of Aldosterone Secretion

- **Angiotensin II** (AT II): potent stimulus
- ↓**Na^+** in blood (Hyponatremia)
- ↑**K^+** in blood (Hyperkalemia)

Acid-Base Balance

- **Aldosterone** is a steroid hormone
  - Derived from cholesterol
  - Can pass through cell membrane
- Enter **α-Intercalated cell**
- Bind to intracellular receptor
- Bind to gene sequences in nucleus to produce:
  - **H^+-ATPase Pump**
    - Expressed at the apical surface: facing lumen
    - **excrete H^+** from tubular cells into the tubular lumen, lose H^+ via the urine → ↓**H^+ in blood**
    - since it is against concentration gradient, it **utilizes ATP**, converting it to ADP and P_i (inorganic phosphate)
- **Aldosterone increases H^+-ATPase Pump**

Electrolyte and Water Balance

Aldosterone

- Aldosterone enters **principal cells** since it is a steroid hormone and can pass the cell membrane
- Bind to intracellular receptor
- Translocate to nucleus and bind to gene sequences that increases expression of the following proteins:
  - **Epithelial Sodium Channel (ENaC)**
    - Convoluted tubule and collecting duct cells are epithelial cells (cuboidal)
    - Apical surface: facing lumen
    - **Na^+ transport into tubular cells** due to concentration gradient (higher Na^+ in lumen than in tubular cell) → ↑**Na^+ in cell**
    - Usually, ENaC and other channels are not present since the late Distal Convoluted Tubule and Collecting Duct will only express ENaC when aldosterone and ADH are present
  - **Na^+/ K^+ ATPase**
    - Present on almost every cell in body
    - Basolateral surface: facing peritubular capillaries
    - Pump **3 Na^+ out** of cell into interstitial fluid and into peritubular capillary
      - ↑**Na^+ in blood**
    - Pumps **2 K^+ from blood into the cell**
      - ↑**K^+ in cell**
  - **K^+ channel**
    - Apical surface: facing lumen
    - K^+ in cell is higher than K^+ in tubular lumen → concentration gradient
    - K^+ in cell move out to the lumen, excreting it via urine → ↑**K^+ in urine**
    - ↓**K^+ in blood**

Antidiuretic Hormone (ADH)

- **Type 2 aquaporins**: regulate water uptake
- Water follows Na^+
- Na^+ moves from the tubular lumen into the blood due to aldosterone
- Water follows the Na^+ from the tubular lumen into the blood
- ↑Na^+ in blood → ↑water reabsorption

Facultative water reabsorption

- dependent on ADH and aldosterone
- increase in water reabsorption due to an increase in Na^+ reabsorption

Summary: Effects of Aldosterone

- Sodium and water reabsorption by facultative process
- K^+ and H^+ excretion to regulate acid-base balance

Table 2. Effects of Aldosterone on Serum Levels of Ions

↑Serum Levels	↓Serum Levels
Na^+	K^+
H_2O	H^+

(C) TYPES OF K^+ SPARING DIURETICS

(1) Aldosterone Blockers

a. **Spironolactone**
b. **Eplerenone**

(2) ENaC and Na+/K+ ATPase Blockers

a. **Triamterene**
b. **Amiloride**

(D) MECHANISM OF ACTION OF K^+ SPARING DIURETICS

- **Recall Normal Physiology:**
  - Aldosterone is released, can be due to low sodium, high potassium, or elevated Angiotensin II
  - Aldosterone gets into cell and binds to intracellular receptor

Aldosterone Blockers Mechanism on

- **Principal cells**
  - **Inhibit binding of aldosterone to the intracellular receptor**
  - ↓aldosterone-intracellular receptor complex that into nucleus
  - ↓stimulation of gene sequences
  - ↓synthesis of transporters
    - ↓ENaC expression
      - ↓Na^+ can move from the tubular lumen into tubular cells
      - ↓Na^+/K^+ ATPase activity
    - ↓Na^+/K^+ ATPase expression
      - ↓Na^+ will be pumped out of the cell and into the blood → **↓Na^+ reabsorption**
      - ↓K^+ movement from blood into cell
    - ↓K^+ channels expression
      - **↓K^+ excretion** via urine
      - **↑K^+ in blood** (potassium-sparing!)
  - Recall: If ADH is present, aquaporins will be expressed allowing water to follow sodium movement via facultative process
    - Since ↓Na^+ reabsorption, **↓water reabsorption**
- **α-Intercalated Cell**
  - **Inhibit binding of aldosterone to the intracellular receptor**
  - ↓aldosterone-intracellular receptor complex that into nucleus→ ↓stimulation of gene sequences
  - ↓synthesis of proteins
  - **↓H^+-ATPase Pump → ↓H^+ excreted → ↑H^+ in blood (acidosis)**

ENaC and Na^+/K^+ ATPase Blockers

- **Block ENaC**
  - ↓Na^+ will move from the tubular lumen into cell
- **Block Na^+/K^+ ATPase**
  - ↓Na^+ will be reabsorbed into the blood
  - ↓K^+ will be pumped into the cell → **↑K^+ in blood**
    - Concentration gradient in the cell and tubular lumen will not be significant since both have low K^+
    - ↓K^+ will move from the cell to the tubular lumen
    - **↓K^+ excreted in the urine**
- **↓Na^+ reabsorption → ↓water reabsorption**
- Do NOT affect H^+-ATPase Pump since they do not affect aldosterone's effect on receptors

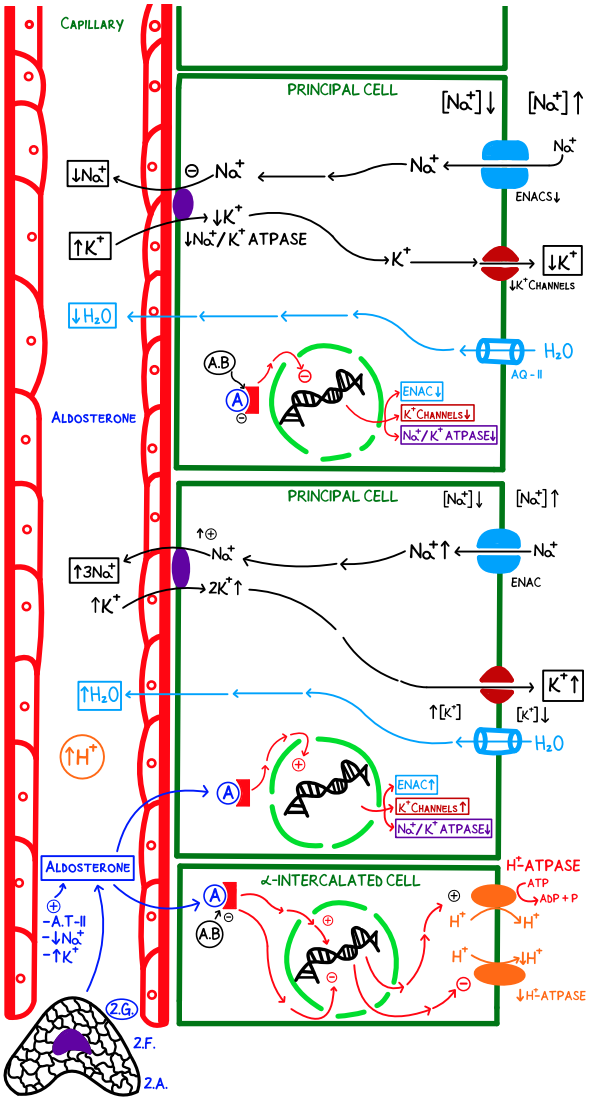

Figure 3. Mechanism of Action of Potassium Sparing Diuretics

II) INDICATIONS

(A) HYPERALDOSTERONISM

(1) Conn Syndrome/ Primary Aldosteronism

- **Tumor in adrenal cortex**
- ↑**aldosterone** secretion
- Management: **Aldosterone blockers** (Spironolactone, Eplerenone)
  - Blocks effect of aldosterone

(B) COMBINED WITH LOOP DIURETICS IN FLUID OVERLOAD STATES

(1) Causes of Fluid Overload States

- **Congestive Heart Failure**
  - Left-sided: pulmonary edema
  - Right-sided: peripheral edema, ascites
- **Cirrhosis**
- **Acute Kidney Injury**
- **Nephrotic syndrome**

(2) Manifestations

- **Pulmonary Edema**
  - Accumulation of fluid in the interstitial spaces between alveoli and pulmonary capillaries
  - Difficulty breathing
- **Peripheral Edema**
  - Accumulation of fluid in the tissue spaces in the leg
  - pain, swelling
- **Ascites**
  - Accumulation of fluid in the abdomen

(3) Mechanism

Recall:

- **Thiazide diuretics** and **loop diuretics** are usually the **mainstay in fluid overload states** since they block more of the sodium and water reabsorption.
- **Potassium-sparing diuretics** act on the end of distal convoluted tubule and collecting duct, only accounting for 2-5% of the sodium and water reabsorption.

(i) Loop diuretics

- act on the thick ascending loop of Henle, inhibiting the reabsorption of **25% of NaCl and water**
- excretes water, NaCl, and **K^+**
- can lead to **Hypokalemia**

(ii) Potassium-sparing diuretics

- **given with loop diuretics** to help **increase K^+** and counteract the excessive K^+ loss caused by loop diuretics to maintain a normal K^+ balance
- can also inhibit NaCl and water reabsorption

(C) HYPERTENSION (IN COMBO WITH THIAZIDES)

Potassium-sparing diuretics

- Inhibit NaCl and water reabsorption
- ↓**NaCl and** ↓**water** → ↓**BV** → ↓**BP**
- Since Potassium-sparing diuretics only account for minor sodium and water reabsorption, they are usually used **in combination with thiazide diuretics**
  - Amiloride/ Triamterene + Hydrochlorothiazide (HCTZ)
  - **Thiazides** can also lead to **hypokalemia**
  - Adding **potassium-sparing diuretics**: added benefit of **inhibiting sodium and water reabsorption** and **prevent potassium drop**

(D) DECREASE MORTALITY IN POST-MI

(1) Post-Myocardial Infarction (Left Ventricle)

- Infarcted cardiac tissue is replaced by fibrous tissue
- Assume anterior MI, ↓**significant pumping function**
- ↓cardiac output → ↓BP
- **Low BP stimulates the baroreceptors** in the aortic arch and the bifurcation of common carotid artery (aortic sinus and carotid sinus)
- Signal medulla to activate **sympathetic nervous system**
- ↑**Norepinephrine release**
  - ↑**Heart rate** (via β-1 receptors)
  - ↑**contractility** of cardiac muscles (via β-1 receptors) → ↑**stress on heart** → cellular adaptation → affect myocardial cells
  - Activates β-1 receptors Juxtaglomerular (JG) cells of **kidney**
    - ↑**Renin**
    - ↑**Angiotensin II (ATII)**
      - ↑Total Peripheral Resistance (TPR) due to intense vasoconstriction → ↑**afterload**
      - ↑ADH and Aldosterone production → ↑sodium and water retention → ↑BV → ↑**preload**

(2) Ventricular Hypertrophy Development

- ↑**stress on heart** (due to ↑HR and ↑contractility)
  - cardiac muscles need to work harder and consume more oxygen → ↑**oxygen demand**
  - But in myocardial infarction, there is low oxygen supply to heart
  - Cardiac cells need to get bigger to adapt to the high oxygen demand → **ventricular hypertrophy**
  - Myocardium becomes thick and larger
- ↑**afterload** (due to ↑AT II → constricting arterioles)
  - Heart needs to work harder to generate higher pressure to push out blood out of ventricles
  - Cardiac cells adapt and become bigger → **ventricular hypertrophy**

(3) Ventricular Dilation Development

- ↑ADH and Aldosterone → ↑Na^+ & H_2O reabsorption → ↑**preload**
  - Stretch myocardium
  - Cellular adaptation → cells grow in series pattern
  - **Ventricular dilation**

(4) Cardiac remodeling

- Process where myocardium undergoes **ventricular dilation or hypertrophy** following a myocardial infarction

(5) Potassium-sparing diuretics

- **Block effect of aldosterone**
  - ↓sodium and water reabsorption
  - ↓BV
  - ↓preload
  - ↓need of cell adaptation
  - ↓**ventricular dilation effect post-MI**
- Especially useful in patients that develop **heart failure** due to severe MI

(E) ELEVATED ANDROGENS

(1) Spironolactone & Eplerenone Effect on Androgens

- In addition to blocking aldosterone, they can also block **androgens**, which are also steroid hormones
- **Normal Physiology of Androgens**
  - Get into cell
  - Bind to intracellular receptor
  - Produce over-all cellular effects
- **Mechanism of Spironolactone and Eplerenone**
  - Inhibit binding of androgen to their intracellular receptor
  - Inhibit cellular effects
  - Used in conditions of elevated androgen levels

(2) Conditions of Elevated Androgens

(i) PCOS (polycystic ovarian syndrome)

- **Due to ↑testosterone**
- Spironolactone → block effects of testosterone
- Manifestations of PCOS:
  - Hirsutism/ ↑hair growth
  - Alopecia
  - Masculinization
  - Oily skin
  - Diabetes: Insulin Resistance

(ii) Androgenic Acne

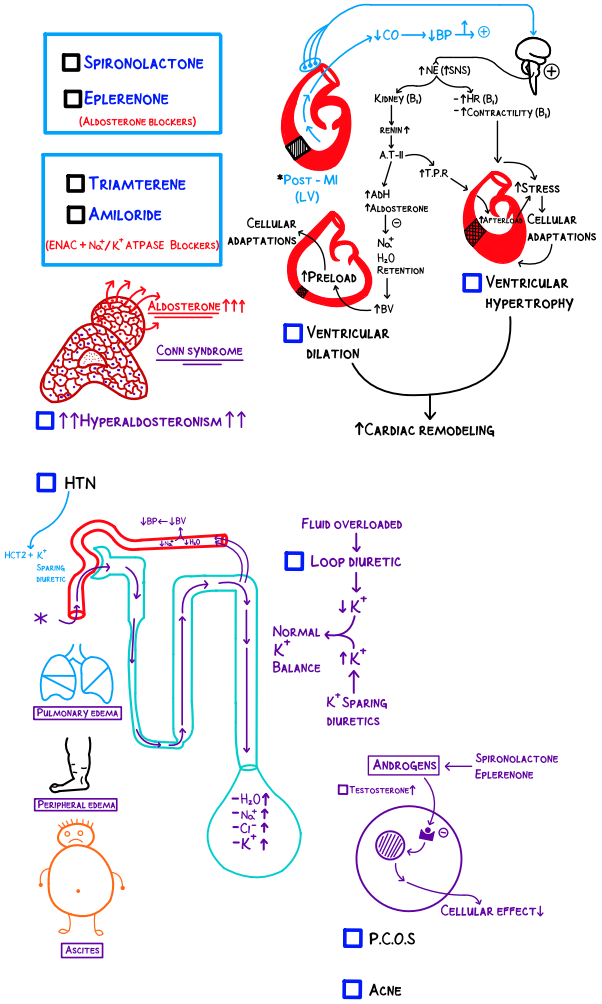

Figure 4. Types and Indications of Potassium Sparing Diuretic

III) ADVERSE REACTIONS

(A) HYPERKALEMIA

- K^+ levels **>5mEq/L**
- **Potassium Sparing** Diuretics
- Block effect of aldosterone, ENaC, or Na^+/K^+ ATPase
- Most concerning of all side effects since it **can lead to arrhythmias**

(1) Recall Normal Physiology

- Na^+ moves into cell from the lumen via ENaC
- Na^+ goes out of cell to the interstitium via Na^+/K^+ ATPase
- K^+ moves into cell from the interstitium via Na^+/K^+ ATPase
- K^+ exits cell into lumen via K^+ transporters

(2) Potassium Sparing Diuretics Mechanism

- Block aldosterone
- ↓Na^+ reabsorption
- ↓Na^+/K^+ ATPase activity
- ↓K^+ entry into cell
- ↓K^+ excretion into urine
- ↑**K^+ in blood**

(3) Interaction with ACE-I and ARB

- ACE-I and ARB **inhibit action of Angiotensin II** (AT II)
  - AT II: stimulus for aldosterone production
- Inhibition of AT II → block aldosterone indirectly
- Leads to same effect as K^+ sparing diuretics
- ↑**K^+ in blood**

(4) Arrhythmias

- High levels of K^+ can cause cardiac arrhythmias that are potentially fatal
- Manifestations on **12-lead EKG**
  - **Peaked T-waves**
  - **Prolonged PR Interval**
    - PR interval: beginning of P wave to the beginning of QRS complex
  - **Wide QRS complex** (>0.12 seconds)
  - **ST- segment depression**
  - **Ventricular Fibrillation**: most dangerous
    - Sine-wave pattern

(B) METABOLIC ACIDOSIS

(1) Recall Aldosterone action on α-Intercalated Cell

- Stimulate H^+-ATPase

(2) Aldosterone Blockers

- Spironolactone, Eplerenone
- **Block H^+-ATPase**
- ↓**H^+ excreted in urine** (excreting less = retaining more)
- ↑**H^+ in blood** → metabolic acidosis

(C) KIDNEY STONES

- Specific to **Triamterene** (Block ENaC and Na^+/K^+ ATPase)
- Unknown underlying mechanism

(D) ACUTE KIDNEY INJURY (AKI)

- Combination of **NSAIDs + Triamterene** induces AKI

(E) ANTI-ANDROGEN EFFECTS IN MALES

- ↓**testosterone**
- ↓**Spermatogenesis**
- **Erectile Dysfunction**
- **Gynecomastia**: enlargement of breast tissues in males

(F) ANTI-ANDROGEN EFFECTS IN FEMALES

- **Alter estrogen and progesterone** levels
- Alter menstrual cycle
- **Amenorrhea**: no menstrual cycle

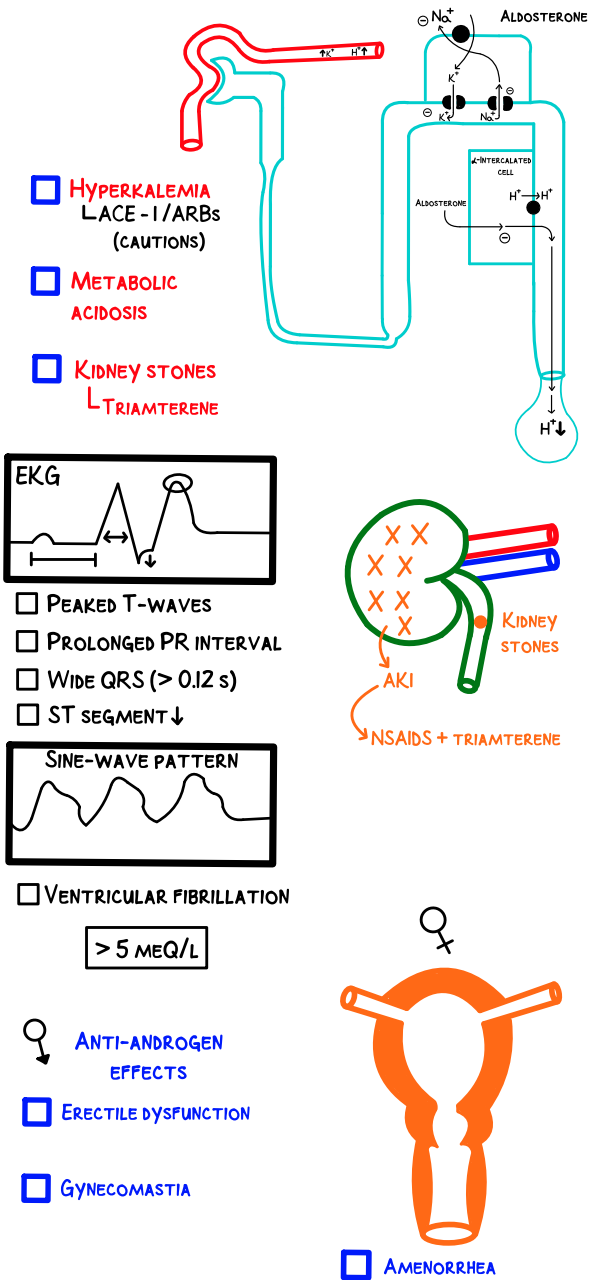

Figure 5. Adverse Reactions of Potassium Sparing Diuretics

IV) REVIEW QUESTIONS

1) **Part of adrenal cortex that secretes aldosterone**
   a. Zona Glomerulosa
   b. Zona Fasciculata
   c. Zona Reticularis
   d. Adrenal Medulla

2) **Site of action of potassium-sparing diuretics**
   a. Ascending limb of Loop of Henle
   b. Proximal Convoluted tubule
   c. End of distal convoluted tubule and collecting duct
   d. Descending limp of Loop of Henle

3) **Stimulants of aldosterone secretion, except:**
   a. AT II
   b. Hypokalemia
   c. Hyperkalemia
   d. Hyponatremia

4) **Which of the following acts by blocking aldosterone?**
   a. Spironolactone
   b. Eplerenone
   c. Triamterene
   d. a and b

5) **Side effects of potassium sparing diuretics, except:**
   a. Hyperkalemia
   b. Anti-androgen
   c. Arrhythmia
   d. Hypertension

6) **Be cautious on giving this with potassium sparing diuretics since it can also cause hyperkalemia**
   a. Loop diuretic
   b. Thiazide diuretic
   c. ACE-I
   d. NSAIDs

7) **A patient is currently taking Spironolactone. He is experience EKG changes with prolonged PR intervals. Which should be the most important lab results that must be checked?**
   a. Calcium
   b. Magnesium
   c. Sodium
   d. Potassium

8) **The patient is taking both aspirin and triamterene. Combination of these medications can lead to what?**
   a. Hypertension
   b. Hyperkalemia
   c. Acute Kidney Injury
   d. Hypokalemia

CHECK YOUR ANSWERS

V) REFERENCES

- Trevor, A., Katzung, B., & Kruidering-Hall, M. (2015). *Katzung & Trevor's Pharmacology Examination & Board Review*. McGraw Hill Education