Heart Failure Pharmacology: Aldosterone Antagonist (Antimineralocorticoid, MCRA)

Aldosterone antagonist are diuretic drugs that used in treatment of congestive heart failure or hypertension and increase survival rate in cardiac patients. They act by competitive antagonism of mineralcorticoid receptors on the distal convoluting tubules and the upper collecting duct of the nephrons. They reduce the edema and workload on heart. Spironolactone is an important and widely used aldosterone antagonist. Other drugs in this category are eplerenone and finerenone.

Overview of Aldosterone Antagonists

Aldosterone antagonists are the specific antagonists that act at the mineralocorticoid receptors, which inhibit sodium resorption in the late distal tubule and the upper collecting duct of the nephron. The principal mineralocorticoid hormone is aldosterone, with its most important biological action: to regulate the fluid and electrolyte balance of the body by promoting Na$^+$ and water retention, as well as the excretion of potassium.

The retention of water induces an increase in plasma volume and an increase in blood pressure. Its secretion is stimulated by angiotensin-II. Aldosterone antagonist interferes with Na$^+$/K$^+$ exchange: potassium excretion is reduced, while Na$^+$ and water excretion is increased. Therefore, it is known as a potassium-sparing diuretic.

1. **Spironolactone**: Most commonly used member of this group.
2. **Eplerenone**: More selective than spironolactone, but less potent and efficacious.
3. **Finerenone**: Non-steroidal; more potent and selective than either eplerenone or spironolactone.

**ACE inhibitors**

- Captopril (Capoten®)
- Enalapril (Vasotec®)
- Lisinopril (Zestril®, Prinivil®)
- Benazepril (Lotensin®)
- Fosinopril (Monopril®)
- Quinapril (Accupril®)
- Perindopril (Aceon®, Coversyl®)
- Trandolapril (Mavik®)

**AA’s (Aldosterone Antagonists)**

- Spironolactone (Aldactone®)

**ARBs (angiotensin receptor blockers)**

- Candesartan (Atacand®)
- Eprosartan (Teveten®)
- Irbesartan (Avapro®)
- Losartan (Cozaar®)
- Olmesartan (Benicar®, Olmetec®)
- Telmisartan (Micardis®)
- Valsartan (Diovan®)

**DRI’s (direct renin inhibitors)**

- Aliskiren (Rasilez®)

<table>
<thead>
<tr>
<th>ACE Inhibitors</th>
<th>ARB’s (angiotensin receptor blockers)</th>
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<tbody>
<tr>
<td><strong>Good antihypertensives</strong></td>
<td><strong>Good antihypertensives</strong></td>
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<tr>
<td>Shown to be beneficial in studies</td>
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<tr>
<td>- <strong>Heart failure</strong></td>
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<tr>
<td>- Microvascular disease (Retinopathy, nephropathy)</td>
<td>- Microvascular disease (Retinopathy, nephropathy)</td>
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<tr>
<td>- Left ventricular hypertrophy</td>
<td>- Left ventricular hypertrophy</td>
</tr>
<tr>
<td>- <strong>Stroke</strong></td>
<td>- <strong>Stroke</strong></td>
</tr>
<tr>
<td>Side Effects</td>
<td>Side Effects</td>
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<tr>
<td>- Hyperkalemia (1 %)</td>
<td>- Hyperkalemia (0.3 %)</td>
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<tr>
<td>- <strong>Cough</strong> (2—20 %)</td>
<td>- <strong>Cough</strong> (0.001 %)</td>
</tr>
<tr>
<td>- Pancreatitis (1 : 5,000)</td>
<td>- Pancreatitis (1 : 15,000)</td>
</tr>
<tr>
<td>- Angioedema (1 : 2,000)</td>
<td>- Angioedema (1 : 20,000)</td>
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**Aldosterone Antagonists**

**Direct Renin Inhibitors**

- Poor antihypertensives, but used as a 4th line drug
- Shown to be beneficial in large studies
- Side effects
  - Hyperkalemia (rare)
  - Feminizing characteristics (due to antiandrogen activity)
- Side effects
  - **Diarrhea**
  - **Headache**

<table>
<thead>
<tr>
<th>Commonly used ACEI and All blockers</th>
<th>Initial daily dose(s)</th>
<th>Target dose</th>
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<tbody>
<tr>
<td><strong>Captopril</strong></td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
</tr>
<tr>
<td><strong>Enalapril</strong></td>
<td>2.5 mg bid</td>
<td>10—20 mg bid</td>
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</table>
Fosinopril | 5—10 mg daily | 40 mg daily
---|---|---
**Lisinopril** | 2.5—5 mg daily | 20—40 mg daily
Perindopril | 2 mg daily | 8—16 mg daily
Quinapril | 5 mg daily | 20 mg bid
**Ramilpril** | 1.25—2.5 mg daily | 10 mg daily
Trandolapril | 1 mg daily | 4 mg daily
**Candesartan** | 4—8 mg daily | 32 mg daily
**Losartan** | 25—50 mg daily | 50—100 mg daily
**Valsartan** | 20—40 mg bid | 160 mg bid

**Mechanism of Action of Aldosterone Antagonists**

**Renin-angiotensin-aldosterone system**

Aldosterone antagonists are competitive aldosterone receptor antagonists, acting primarily at the **aldosterone-dependent Na⁺-K⁺ exchange site** in the **late distal tubule and upper collecting tubule**. Normally, aldosterone binds with the aldosterone (mineralocorticoid) receptors to form the **aldosterone-induced proteins (AIPs)**. These
proteins promote the sodium reabsorption and K⁺ secretion.

Aldosterone antagonist prevents the binding of aldosterone at the mineralocorticoid receptors, resulting in the **failure of production of mediator protein (AIPs)**; thus, the **antagonist-receptor complex** inhibits the exchange of Na⁺ for K⁺ and H⁺ ions; eventually increases the excretion of Na⁺ and water, **while conserving K⁺ and H⁺ ions**.

### Spironolactone

Spironolactone is a steroid aldosterone antagonist chemically related to the aldosterone; competitively binding to the aldosterone receptor at the **late distal tubule and upper collecting tubule** of the **nephron**.

### Pharmacokinetics

- Spironolactone undergoes rapid and extensive hepatic metabolism
- Major compounds metabolites are **sulfur-containing products** e.g. 7-alpha-thiomethyl-spirolactone (TM) and canrenone (CAN)
- Together with spironolactone, these major metabolites are thought to be primarily responsible for the therapeutic effects of the drug
- Plasma protein binding capacity is more than 90 %
- Excreted mainly in the urine, and also in bile
- Food increases the bioavailability of unmetabolized spironolactone almost by 100 %

### Pharmacological Action of Spironolactone

Spironolactone acts as both **diuretics** and as **antihypertensive**. It can be used as **monotherapy, or in combination with other diuretics**, which act on the proximal part of the renal tubule.

- In primary and secondary **hyperaldosteronism** (e.g. **congestive cardiac failure** (CCF), **liver cirrhosis**, and **nephrotic syndrome**), there is increased levels of the mineralocorticoid i.e. aldosterone production. Spironolactone competitively blocks the aldosterone receptor binding sites, thus providing effective management against **edema and ascites**.
- In a patient with **primary hyperaldosteronism**, spironolactone is also
Effective against hypertension (HTN), in lowering both systolic and diastolic blood pressure.

- In most of the cases of essential hypertension, spironolactone provides effective therapy by inhibiting the exchange of Na\(^+\) for K\(^+\) in the distal convoluted tubule and helps to prevent potassium loss.

### Indication

- Used as adjunctive therapy, in combination with K\(^+\) losing diuretics, for the management of hypertension, and chronic heart failure (NYHA class III-IV)
- Primary aldosteronism e.g. **Conn’s syndrome**
- **Refractory edema**
- **Secondary aldosteronism** due to nephritic syndrome, cardiac failure, liver cirrhosis
- Hypokalemia
- Treatment of **acne vulgaris**

### Contraindication

- Anuria
- Hyperkalemia
- **Acute renal failure**
- Significant impairment of renal excretory function
- **Addison’s disease**
- Concomitant use with other aldosterone antagonists e.g. eplerenone

### Side Effects

- Electrolyte imbalance: Hyperkalemia, hyponatremia
- Endocrinopathy e.g. **gynecomastia**, **impotence**, benign prostatic hyperplasia, amenorrhoea, etc.
- Hyperchloremic metabolic acidosis in cirrhotic patient
- **Acute renal failure**
- GIT upset like mild nausea, vomiting, diarrhea, gastric bleeding, **gastritis** and ulceration
- Hematologic: Agranulocytosis
- Hypersensitivity reaction: Fever, urticaria, anaphylactic reactions and vasculitis

### Summary of Adult and Pediatric Dose of Spironolactone in Various Conditions

<table>
<thead>
<tr>
<th>Spironolactone</th>
<th>Disease</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
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<tbody>
<tr>
<td></td>
<td><strong>Congestive cardiac failure</strong></td>
<td>25 mg/day, orally</td>
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<tr>
<td><strong>Hypertension</strong></td>
<td>25 to 200 mg/day; orally in 1 or 2 divided doses.</td>
<td>Neonates: 1 to 3 mg/kg/day, orally every 12 to 24 hours Children: 1.5 to 3.3 mg/kg/day, orally in divided doses every 6 to 12 hours, not more than 100 mg/day</td>
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### Drug Interactions

- **Spironolactone & digoxin:** Increase half-life of digoxin resulting in increased serum digoxin levels and subsequent digitalis toxicity. Thus, the patient should be carefully monitored to avoid over- or under-digitalization.
- **Spironolactone & ACE inhibitors:** Produces severe hyperkalemia
- **Spironolactone & non-steroidal anti-inflammatory drugs (NSAIDs):** Combination has been associated with severe hyperkalemia. NSAIDs can reduce the antihypertensive, diuretic and natriuretic effect of spironolactone
- **Spironolactone & corticosteroids (ACTH):** Intensified electrolyte depletion, particular hypokalemia may occur
- **Spironolactone & alcohol, barbiturates, or narcotics:** Potentiation of orthostatic hypotension may develop
- **Spironolactone & lithium:** High risk of lithium toxicity as renal clearance of lithium is reducing

### Precautions

- Potassium supplementation e.g. potassium rich fruits, food or drugs, should not be given with spironolactone therapy; this may lead to hyperkalemia in the patients
- Spironolactone should not be given concomitantly with other potassium-sparing diuretics
- Patients should be monitored for the evidence of fluid or electrolyte imbalance, e.g. hyponatremia, hyperkalemia and hypomagnesemia
- Patient lipid profile should be assessed

### Eplerenone

Eplerenone is a steroid and more selective anti-mineralocorticoid, but less potent and
efficacious than spironolactone. It is advantageous over spironolactone as it causes fewer side effects like gynecomastia (1 % case), impotence and amenorrhea.

Indication

- Hypertension
- Congestive cardiac failure

Adult Dose of Eplerenone

A. Congestive Cardiac Failure: Initially 25 mg orally once daily. Dosage should be adjusted to a maximum dose of 50 mg once daily, preferably within 4 weeks.
B. Hypertension: 50 mg orally once daily; if inadequate response then the dose should be increased to 50 mg twice a day.

Contraindication

- Known hypersensitivity to eplerenone
- Severe kidney disease
- High blood potassium levels
- Hypertension with type 2 diabetes with proteinuria
- In combination with other drugs such as clarithromycin, itraconazole, ketoconazole, or ritonavir
- With potassium supplementation or potassium-sparing diuretics (e.g. amiloride, spironolactone, triamterene)

Side Effects

- Severe hypersensitivity reactions (itching, rash, difficulty in breathing; tightness in the chest; swelling of the lips, tongue or face)
- CNS: Dizziness, tiredness, and headache
- Metabolic: Hyperkalemia (> 5.5 mEq/L), hypercholesterolemia and hypertriglyceridemia
- Endocrine system: Gynecomastia (1 % case) and mastodynia (1.3 % case), abnormal vaginal bleeding in females may occur
- CVS: Fast or irregular heartbeat, chest pain
- GIT: Nausea, vomiting, and severe or persistent diarrhea
- Renal: Albuminuria resulting in the swelling of the legs, ankles, or feet

Finerenone
Finerenone is a non-steroidal aldosterone receptor antagonist, which inhibits the physiological effects of aldosterone. Like other aldosterone antagonists (e.g. spironolactone, eplerenone), finerenone is not a steroid, but a derivative of dihydropyridine.

Finerenone has a relatively less affinity to steroid hormone receptors than spironolactone and eplerenone, which results in fewer side effects like impotence, decrease libido and gynecomastia.

Review Questions

The solutions are located below the sources.

1. Which one of the following is a K⁺ sparing diuretic?
   - A. Spironolactone
   - B. Frusemide
   - C. Acetazolamide
   - D. Torasemide
   - E. Clopamide

2. Which of the following drug-side effect combinations are correct?
   - A. Spironolactone – Hypokalemia
   - B. Spironolactone – Hyperkalemia
   - C. Eplerenone – Ototoxicity
   - D. Spironolactone + ACE inhibitors – Hypokalemia
   - E. Spironolactone – Hyperchloremic metabolic alkalosis

3. Aldosterone antagonists act on which part of the nephron?
   - A. Bowman’s capsule
   - B. Proximal convoluted tubule
   - C. Descending limb of loop of Henle
   - D. Ascending limb of loop of Henle
   - E. Distal convoluted tubule and collecting duct
References


**Correct answers:** 1A, 2B, 3E

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Notes