Pharmacology – I [PHL 313]

Diuretics

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Renal Pharmacology

Kidneys:

• Each adult kidney weighs 125-170g in males and 115-155g in females, represent 0.5% of total body weight, but receive ~25% of the total arterial blood pumped by the heart.

• Each kidney contains 1-2 million nephrons:
  – The glomerulus
  – The proximal convoluted tubule
  – The loop of Henle
  – The distal convoluted tubule
The formation of urine

In summary, three processes occurring in successive portions of the nephron accomplish the function of urine formation:

- **Filtration** of water and dissolved substances out of the blood in the glomeruli and into Bowman's capsule;

- **Reabsorption** of water and dissolved substances out of the kidney tubules back into the blood (note that this process prevents substances needed by the body from being lost in the urine);

- **Secretion** of hydrogen ions (H\(^+\)), potassium ions (K\(^+\)), ammonia (NH\(_3\)), and certain drugs out of the blood and into the kidney tubules, where they are eventually eliminated in the urine.
**Proximal convoluted tubule**
Reabsorption of water, ions, and all organic nutrients

**Distal convoluted tubule**
- Secretion of ions, acids, drugs, and toxins
- Variable reabsorption of water, sodium ions, and calcium ions (under hormonal control)

**NEPHRON**
- Capsular space
- Glomerulus
- Efferent arteriole
- Afferent arteriole
- Bowman’s capsule

**Renal corpuscle**
Production of filtrate

**Loop of Henle**
- Further reabsorption of water (descending limb) and both sodium and chloride ions (ascending limb)

**COLLECTING SYSTEM**
- Collecting duct
  - Variable reabsorption of water and secretion of sodium, potassium, hydrogen, and bicarbonate ions
- Papillary duct
  - Delivery of urine to minor calyx
Diuretics

- **DIURESIS**: increased urine flow
- **DIURETICS**: substances which elicit diuresis
- In the kidney, water reabsorption dependent primarily on Na\(^+\) reabsorption
- Thus, a diuretic is an agent which inhibits tubular Na\(^+\) reabsorption (along with Cl\(^-\), HCO\(_3\)\(^-\)), at one or more sites in nephron, resulting in increased excretion of these ions.
- Natriuretic effect (enhance secretion of sodium and thus water)
- Diuretics can have effects on:
  - Sodium reabsorption
  - Potassium loss
  - Body fluids
• Certain disease states may cause blood volume to increase outside of narrowly defined limits
  – Hypertension
  – Congestive heart failure
  – Liver cirrhosis
  – Nephrotic syndrome
  – Renal failure
• Dietary Na restriction often not enough to maintain ECF and prevent edema $\rightarrow$ diuretics needed
• Primary effect of diuretics is to increase solute excretion, mainly as NaCl
• Diuretics causes **increase** in urine volume due to increased osmotic pressure in lumen of renal tubule and concomitant **decrease** in extra-cellular volume (blood volume)
The different classes and key prototypes of diuretics include:

- **Osmotic diuretics:**
  - Mannitol

- **Carbonic anhydrase inhibitors:**
  - Acetozolamide

- **Loop diuretics or the high ceiling diuretics:**
  - Furosemide, Torsemide, Bumetanide, Ethacrynic acid

- **Thiazide and thiazide-like diuretics:**
  - Hydrochlorothiazide, Chlorthalodone, chlorothiazide, Metolazone

- **K⁺ sparing diuretics:**
  - Na channel inhibitors: amiloride, triamterene
  - Aldosterone receptor antagonists: spironolactone, eplerenone
Nephron: sites of action of diuretics

Site of diuretic action:
- Carbonic anhydrase inhibitors
- Osmotic diuretics
- Loop diuretics
- Thiazide diuretics
- K⁺-sparing diuretics

Osmotic diuretics

- **Therapeutic Uses:**
  - Acute renal failure
  - Reduce preoperative intraocular or intracranial pressure
- No interaction with transport systems
- Consequently solutes remain within the filtrate and exert an osmotic effect that inhibits the reabsorption of water.
  - This effect can also be seen if blood plasma levels of glucose become very high (e.g. in hyperglycaemic episodes experienced by individuals with diabetes mellitus). The glucose that remains unabsorbed inhibits the reabsorption of water and larger volumes of urine are typically produced, initially.
- All activity depends on osmotic pressure exerted in lumen
- Blocks water reabsorption in **PCT & descending loop of Henle**
- Results in large water loss, smaller electrolyte loss → can result in hypernatremia
Carbonic anhydrase inhibitors: work in PCT

**Example**: Acetazolamide

- Acts to block carbonic anhydrase (CA),
- CAIs work on co-transport of Na\(^+\), HCO\(_3^-\) and Cl\(^-\) that is coupled to H\(^+\) counter-transport

1. CA converts HCO\(_3^-\) + H\(^+\) to H\(_2\)O + CO\(_2\) in tubular lumen
2. CO\(_2\) diffuses into cell (water follows Na\(^+\)), CA converts CO\(_2\) + H\(_2\)O into HCO\(_3^-\) + H\(^+\)
3. H\(^+\) now available again for counter-transport with Na\(^+\), etc)
4. Na\(^+\) and HCO\(_3^-\) now transported into peritubular capillary

- CA can catalyze reaction in either direction depending on relative concentration of substrates
Therapeutic Uses

– Cystinuria (increase alkalinity of tubular urine)
– Glaucoma (decrease ocular pressure)
– Acute mountain sickness
– Metabolic alkalosis
Na-K-2Cl SYMPORT INHIBITORS

Also Called:
- Loop Diuretics
- High Ceiling Diuretics

Furosemide
(LASIX)

Bumetanide
(BUMEX)

Torsemide
(DEMADEX)

Ethacrynic Acid
(EDECRIN)
MOA: Loop diuretics

- No transport systems in descending loop of Henle
- Ascending loop contains Na\(^+\) - K\(^+\) - 2Cl\(^-\) co-transporter from lumen to ascending limb cells
- Loop diuretic blocks co-transporter $\Rightarrow$ Na\(^+\), K\(^+\), and Cl\(^-\) remain in lumen, excreted along with water
Loop diuretics (ascending limb of loop)

- Generally cause greater diuresis than thiazides; used when they are insufficient
- Can enhance Ca\(^{2+}\) and Mg\(^{2+}\) excretion

**Therapeutic uses:**
- Hypertension, in patients with impaired renal function
- Congestive heart failure (moderate to severe)
- Acute pulmonary edema
- Chronic or acute renal failure
- Nephrotic syndrome
- Hyperkalemia
- Chemical intoxication (to increase urine flow)
Therapeutic Effects

- Increase Na Excretion to 25% of Filtered Load
- Increase Urine Volume
- Increase Ca Excretion
- Impair Free Water Reabsorption
- Increase Venous Capacitance

Treatment for:
- Severe Edema
- Oliguric Acute Renal Failure
- Hypercalcemia
- Hyponatremia
- Pulmonary Edema

Severe Edema
Oliguric Acute Renal Failure
Hypercalcemia
Hyponatremia
Pulmonary Edema
ADVERSE EFFECTS

- Profound ECFV Depletion
- Hypokalemia
- Hypocalcemia
- Hypomagnesemia
- Metabolic Alkalosis
- Ototoxicity
- Hyperuricemia
- Hyperglycemia
Na-Cl SYMPORT INHIBITORS

Also Called:
• Thiazide Diuretics
• Thiazide-Like Diuretics

Hydrochlorothiazide (HYDRODIURIL)
Chlorthalidone (HYGROTON)
Chlorothiazide (DIURIL)
Metolazone (ZAROXOLYN)
MOA: Thiazide Diuretics in the DCT

- Less reabsorption of water and electrolytes in the distal convoluted tubule than proximal tubule or loop
- A Na\(^+\)-Cl\(^-\) co-transporter there is blocked by thiazides
Thiazide diuretics (DCT)

- Magnitude of effect is lower because work on distal convoluted tubule (only receives 15% of filtrate)
- Cause decreased Ca excretion → hypercalcemia → reduce osteoporosis
- Therapeutic uses
  - Hypertension
  - Edema (Cardiac, hepatic, Renal)
  - Congestive heart failure (mild)
  - Renal calculi
  - Nephrogenic diabetes insipidus
  - Chronic renal failure (as an adjunct to loop diuretic)
  - Osteoporosis
THERAPEUTIC EFFECTS

Increase Na Excretion to 5% of Filtered Load

Treatment for Hypertension

Treatment for Nephrogenic Diabetes Insipidus

Treatment for Mild Edema

Decrease Ca Excretion

Treatment for Calcium Nephrolithiasis
ADVERSE EFFECTS

- Hypomagnesemia
- Metabolic Alkalosis
- Hypokalemia
- ECFV Depletion
- Impotence
- Hyponatremia
- Increased LDL
- Hyperuricemia
- Hypercalcemia
- Hyperglycemia
- Hyponatremia
Na CHANNEL INHIBITORS

Also Called:
• K-Sparing Diuretics

Tiamterene  
(DYRENIUM)

Amiloride  
(MIDAMOR)
MOA:

Two cell types in collecting tubule

1. Principal cells – transport Na, K, water
2. Intercalated cells – secretion of $\text{H}^+$ and $\text{HCO}_3^-$
3. Blocking Na+ movement in also prevents K+ movement out
Potassium-sparing diuretics (collecting tubule)

- Reduce K loss by inhibiting Na/K exchange
- Not a strong diuretic because Have most downstream site of action (collecting tubule)
- Often used in combination with thiazide diuretics to restrict K loss
- **Therapeutic uses**
  - Chronic liver failure
  - Congestive heart failure, when hypokalemia is a problem
THERAPEUTIC EFFECTS

- Enhance Natriuresis Caused by Other Diuretics
- Prevent Hypokalemia
- Block Na Channels
- Used in Combination with Loop & Thiazide Diuretics
- Treatment for Liddle’s Syndrome
- Treatment for Lithium-Induced Diabetes Insipidus
ADVERSE EFFECTS

Amiloride

- Hyperkalemia

Triamterene

- Hyperkalemia
- Renal Stones
- Interstitial Nephritis
- Megaloblastosis

Renal Stones

Interstitial Nephritis

Megaloblastosis
MINERALOCORTICOID RECEPTOR ANTAGONISTS

Also Called:
- K-Sparing Diuretics
- Aldosterone Antagonists

Spironolactone (ALDACTONE)

Eplerenone (INSPRA)
LATE DISTAL TUBULE AND COLLECTING DUCT

(Syndrome of Apparent MC excess)
(Licorice: Glycyrrhizic Acid)
THERAPEUTIC EFFECTS

Enhances Natriuresis Caused by Other Diuretics
Prevents Hypokalemia
Blocks Aldosterone

Used in Combination with Loop & Thiazide Diuretics

Treatment for Primary Hyperaldosteronism
Treatment for Edema of Liver Cirrhosis
Treatment for Hypertension
Treatment for Heart Failure
ADVERSE EFFECTS

- Hyperkalemia
- Gastritis
- Metabolic Acidosis
- Peptic Ulcers
- Impotence
- Deepening of Voice
- CNS Side Effects
- Hirsutism
- Gynecomastia
- Menstrual Irregularities
# Types and Names of Diuretics

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<th>Example</th>
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<td>Osmotic agents</td>
<td>Mannitol</td>
<td>PCT</td>
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<td>Descending loop</td>
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<td>Carbonic anhydrase inhibitors</td>
<td>Acetazolamide</td>
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<td>Loop diuretic</td>
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<td>K⁺ - sparing</td>
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Thank you