Chapter 15   Diuretic Agents
Diuretics

• Diuretics are agents that increase the rate of urine formation and salt excretion.

• “Diuresis” = increased water formation, but the term is also used to indicate increased salt excretion.
Superficial nephrons (87%)
Juxtamedullary nephrons (~13%)

Osmolality (mOsm)
300
300
300
300
500
500
700
700
900
900
1200
1200

Cortex
Outer Medulla
Inner Medulla
Papilla
Secretion of $A^-$, $BH^+$ of bound and unbound drug

Filtration @ Bowman’s capsule

Proximal tubule (PT)

Descending thin limb (DTL)

Ascending thin limb (ATL)

Thick ascending limb (TAL)

Distal tubule (DT)

Collecting tubule (CT)
Secretion of $A^-$, $BH^+$ of bound and unbound drug

Filtration @ Bowman’s capsule

Proximal tubule (PT)

Descending thin limb (DTL)

Ascending thin limb (ATL)

Distal tubule (DT)

Collecting tubule (CT)

Thick ascending limb (TAL)
Water conservation and elimination

- The water-permeable segments of the tubule are:
  - PT
  - DTL
  - CT (including the late distal tubule)

- The water-impermeable segments are:
  - ATL
  - TAL
  - DT
  - This region is known as the diluting segment/region of the tubule

- As Na+ is reabsorbed by transport processes in the water-impermeable diluting segment, “free water” is produced, *i.e.*, a hypoosmotic TF is produced

- CT under influence of ADH
  - +ADH – much of the generated “free water” is reabsorbed; a concentrated (hyperosmotic) urine is produced
  - -ADH – a dilute (hypoosmotic) urine is produced; subject is “water-loaded”
Review of Kidney Function

• Renal blood flow (RBF) \( \approx 1300-1400 \text{ ml min}^{-1} \) and assuming a hematocrit of 0.5
• Renal plasma flow (RPF) \( \approx 650-700 \text{ ml min}^{-1} \)

• The glomerular filtration rate (GFR) \( \approx 130 \text{ ml min}^{-1} \) and, therefore, fraction of RPF filtered at the glomerulus \( = \text{FF} = 20\% \)

• Normal urine production rate \( \approx 1 \text{ ml min}^{-1} \), which indicates that 129/130 (>99%) of filtered plasma (tubular fluid) is reabsorbed

• >99% of filtered load of salt is reabsorbed
Normal Kidney Function (continued)

- >99% of glomerular ultrafiltrate reabsorbed along the tubule
  - >99% of salt in TF is reabsorbed
  - >99% of H₂O is reabsorbed
- Staggering energy cost
  - Kidneys make up 0.5% of BW; however, kidneys consume 7% of total body O₂, most of which is consumed in ATP production
- ATP drives the Na⁺ pump for reabsorption of Na⁺ throughout the tubule; Na⁺ reabsorption is the driving force for the reabsorption of water
Distal tubule (DT)

1. 5-10% of filtered load of Na⁺ reabsorbed

2. Na⁺ pump (basolateral)
   Na⁺,Cl⁻ cotransporter

3. Ca²⁺ reabsorption (PTH-dependent)

4. H₂O impermeable
Collecting tubule (CT) and late distal tubule

1. 2-5% of filtered load of Na⁺ reabsorbed
2. Na⁺ pump (basolateral)
   Na⁺-selective channels (luminal)
   K⁺, H⁺ secretion
3. H₂O permeable, +ADH
   H₂O impermeable, -ADH
4. Na⁺ reabsorption
   ↑ +ALD
   ↓ +ANP
Paracelsus (1493-1541) – discovered use of “calomel”, HgCl, as a diuretic for treatment of edematous states
  1900-1910 – merbaphen
  1924-1950s – mersalyl
1940s – diuretic effect of the antibiotic sulfanilamide lead to the discovery of the carbonic anhydrase inhibitors (CAIs), a class of diuretics
1950s – CAIs led to the discovery of the thiazide class of diuretics
1960s – discoveries of the loop diuretics, K⁺-sparing diuretics, and spironolactone (K⁺-sparing)
Some Uses of Diuretics

1. ↓ Edema
   a. Congestive heart failure
   b. Hepatic cirrhosis with ascites
   c. Renal disease/nephrotic syndrome
2. Maintenance of urine flow
   a. Circulatory shock
   b. Surgical procedures
   c. ↓ Toxic effects of poisons filtered or secreted into the renal tubules
3. Hypertension
4. Nephrogenic diabetes insipidus
5. Nephrolithiasis (renal stones)
6. Hypercalcemia
7. Glaucoma
8. Altitude sickness
Diuretic Agents

1. Osmotic diuretics
2. Carbonic anhydrase inhibitors (CAIs)
3. Loop diuretics (Na\(^+\),K\(^+\),2Cl\(^-\) transporter)
4. Thiazide diuretics Na\(^+\),Cl\(^-\) transporter)
5. K\(^+\)-sparing diuretics
   a. Na\(^+\)-channel blockers
   b. Mineralocorticoid receptor (MR) antagonist
Osmotic Diuretics
“Typical” urinary excretion patterns. Data are representative of responses in man or large dog under conditions of normal acid-base balance and hydration. Excretion rates represent values observed at peak diuresis after a maximally effective dose.

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Mechanism of action of osmotic diuretics

1. Expand ECFV, decreases $[\text{Na}^+]_{\text{plasma}}$ and $[\text{Na}^+]_{\text{TF}}$

2. Act all along the tubule, both in water-permeable and water-impermeable segments

   a. Water-permeable segments – osmotic diuretic
      “obligates” more H$_2$O to the tubule, i.e., produces
      “counter-osmotic force” and hinders H$_2$O
      reabsorption

   b. Water-permeable and -impermeable segments –
      because of ECFV expansion, $[\text{Na}^+]_{\text{TF}}$ is reduced,
      and $[\text{Na}^+]_{\text{TF}}/[\text{Na}^+]_{\text{intracellular}}$ gradient is less; therefore,
      $\text{Na}^+$ reabsorption via apical (luminal) processes along
      the tubule is decreased, and $\text{Na}^+$ excretion is increased
Osmotic Diuretics

Mannitol
Urea

Uses
1. Acute renal failure (ARF) – mannitol is a suitable alternative to a loop diuretic for ARF caused by obstructing tubular casts (precipitated hemoglobin, myoglobin), nephrotoxins, or swelling of tubular elements.
2. Maintenance of urine flow, e.g., during open heart or vascular surgery
3. Glaucoma (↓ intraocular pressure)
4. ↓ Cerebral edema

Toxicity
1. Can lead to CHF/pulmonary edema
2. Osmotic diuretics cause loss of water in excess of electrolytes
   a. ↑ $[\text{Na}^+]_{\text{plasma}}$
   b. dehydration
3. $K^+$-wasting
Mechanism of $K^+$-wasting

Lumen-urine

Collecting tubule

Interstitium-blood

Principal cell

$Na^+$

Lumen (-) potential

$K^+$

$CT$ (slow)

$ATP$
Carbonic Anhydrase Inhibitors (CAIs)
“Typical” urinary excretion patterns. Data are representative of responses in man or large dog under conditions of normal acid-base balance and hydration. Excretion rates represent values observed at peak diuresis after a maximally effective dose.

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Carbonic Anhydrase Inhibitors (CAIs)

Acetazolamide

Uses

1. glaucoma – most common indication for CAIs

**dorzolamide, brinzolamide** – topical CAIs; reduce intraocular pressure comparable to oral agents, but show **no diuretic effect** and **no systemic metabolic effect** (e.g., no alkalinization of urine; no metabolic acidosis)

2. acute mountain sickness (altitude sickness)
3. treatment of metabolic alkalosis

Toxicity

1. metabolic acidosis
2. renal stones (Ca^{2+} salts insoluble in alkaline TF)
3. K⁺-wasting
4. sulfonamide hypersensitivity/photosensitivity reactions
CAI/Mechanism of $K^+$-wasting

Lumen-
urine

Collecting
tubule

Interstitium-
blood

Principal cell

$Na^+$

$Na^+$

$K^+$

$K^+$

Lumen (-) potential
(-50mV)

$\text{HCO}_3^-$

(very slow)

ATP
Loop Diuretics
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Loop Diuretics

**Furosemide**

**Bumetanide**

**Torsemide**

**Uses**

1. CHF
2. edema (pulmonary, hepatic cirrhosis, nephrotic syndrome, ascites)
3. ARF
4. hypercalcemia

**Toxicity**

1. overzealous use → serious depletion of body Na+, or ↓ ECFV → circulatory collapse and thromboembolic episodes
2. ↑ K⁺ excretion → cardiac arrhythmias
   ↑ H⁺ excretion → metabolic alkalosis
3. ↑ Ca²⁺ excretion
   ↑ Mg²⁺ excretion
4. ototoxicity, e.g., deafness, tinnitus, etc., - loop diuretics act on a Na⁺,K⁺,2Cl⁻ co-transporter in the inner ear to disturb electrolyte balance (this toxicity is not seen with other classes of diuretics)
5. hyperuricemia → gout
6. diabetes mellitus by causing hyperglycemia
7. sulfonamide hypersensitivity/photosensitivity reactions
Mechanism of $K^+$-wasting

Lumen–urine

Collecting

tubule

Interstitium–

circulation

Principal cell

$Na^+$

$Na^+$

Lumen (−) potential

$K^+$

ATP

$CT$

(slow)

$K^+$
**“Typical” urinary excretion patterns.** Data are representative of responses in man or large dog under conditions of normal acid-base balance and hydration. Excretion rates represent values observed at peak diuresis after a maximally effective dose.

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Thiazide Diuretics

Hydrochlorothiazide
Metolazone

Uses

1. hypertension
2. CHF
3. edema (pulmonary, hepatic cirrhosis, nephrotic syndrome)
4. diabetes insipidus (paradoxical effect → ↓urine volume ~50%)
5. renal stones - ↑Ca²⁺ reabsorption in distal tubule

Toxicity

1. ↑K⁺ excretion → cardiac arrhythmias
   ↑H⁺ excretion → metabolic alkalosis
2. metabolic alkalosis
3. ↑plasma urate → gout
4. hyperglycemia (diabetes) – impaired pancreatic release of insulin
5. hyperlipidemia (5-15% ↑cholesterol and LDL)
6. sulfonamide hypersensitivity/photosensitivity reactions
Mechanism of $K^+$-wasting

Lumen-
urine

Collecting
tubule

Interstitium-
blood

Principal cell

$Na^+$

$Na^+$

ATP

$K^+$

$K^+$

Lumen (-) potential

$Cl^-$

(slow)
K+-sparing and Mineralocorticoid Diuretics
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K⁺-sparing Diuretics

Na⁺-channel blockers

- Triamterene
- Amiloride

Uses

1. combination therapy: augment diuretic and anti-hypertensive effects of loop and thiazide diuretics; and, offset the kaliuretic effects (K⁺-wasting) of loop and thiazide agents.

2. aerosolized amiloride improves mucociliary clearance in patients with cystic fibrosis

3. useful for treatment of Li⁺-induced nephrogenic diabetes insipidus – blocks Li⁺ entry through Na⁺-channels of the collecting tubule

Toxicity

1. hyperkalemia - life-threatening !!!
K⁺-sparing Diuretics

Aldosterone antagonists

Spironolactone

Uses

1. combination therapy (see above)

2. particularly useful in primary aldosteronism (adrenal adenomas or hyperplasia) and in secondary aldosteronism (CHF, hepatic cirrhosis, ascites, nephrotic syndrome) – drug of choice in hepatic cirrhosis.


Toxicity

1. hyperkalemia - life-threatening !!!
Diuretic-associated drug-drug interactions (DDIs)

1. Diuretic-induced $K^+$-wasting may cause fatal quinidine-induced arrhythmias

2. Diuretic-induced $K^+$ and $Mg^{2+}$-wasting may potentiate digitalis-induced arrhythmias

3. NSAIDs attenuate diuretic drug responses

4. Diuretics increase plasma concentrations of co-administered drugs and cause DDIs:
   - aminoglycosides
   - anticoagulants
   - digitalis glycosides
   - $Li^+$
   - aspirin (high-dose therapy)
   - propranolol
   - sulfonyleureas
   - amphotericin B
Algorithms for Diuretics

**ARF** (Renal insufficiency)
1) Loop
2) Add Thiazide
   If inadequate
3) Dialysis

**Nephrotic syndrome**
1) Loop
2) Add Thiazide
3) Add K⁺-sparing

**Cirrhosis**
1) Spironolactone
2) Cl<sub>Cr</sub> > 50 ml/min
   Add thiazide
   Or, If Cl<sub>Cr</sub> < 50 ml/min
2) Add Loop
If $\text{ClCr} < 50 \text{ ml/min}$

1) If $\text{ClCr} < 50 \text{ ml/min}$
   Loop

2) Add thiazide if response inadequate

3) $\text{K}^+\text{-sparing}$

If $\text{ClCr} > 50 \text{ ml/min}$

1) If $\text{ClCr} > 50 \text{ ml/min}$
   Thiazide

2) *Substitute loop if response inadequate

3) $\text{K}^+\text{-sparing}$

1) Loop

2) Add thiazide if response inadequate

3) $\text{K}^+\text{-sparing}$

*Substitute loop if response inadequate
Dilated Cardiomyopathy

Left Ventricular Dysfunction → inotropic agents

? → perceived reduction in circulating volume/pressure

→ vasoconstriction
→ salt and water retention

→ ↑ sympathetic tone
→ ↑ renin-angiotensin-aldosterone
→ ↑ arginine vasopressin

vasodilators
- diuretics
- DA1 agonists
- ANF

sympatholytic agents
- beta blockers
- ACE inhibition
- AVP antagonist
Homeostasis of Blood Volume and Pressure

Low Blood Pressure
Low Blood Volume

Renin

Angiotensinogen

Angiotensin I

Converting enzyme (kininase II)

Angiotensin II

Vasoconstriction

Aldosterone secretion

Sodium retention

Increased Blood Pressure

Increased Blood Volume

(1) β-adrenergic blockers (inhibit renin release), (2) converting enzyme inhibitors, (3) competitive antagonist A-II, (4) aldosterone antagonist, (5) vasodilators, (6) diuretics.
Questions

• Please describe the classification of diuretics, the classic drugs as well as the mechanisms?

• Please describe the clinical application and adverse reaction of loop diuretic and thiazide diuretic?