DIURETICS

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Diuretics

• A diuretic is a drug that increases the secretion of urine (ie, water, electrolytes, and waste products) by the kidneys.

• Many conditions or diseases, such as hypertension, congestive heart failure, endocrine disturbances, and kidney and liver diseases can cause retention of excess fluid (edema).

• A diuretic is used when the patient shows signs of excess fluid retention.

• Reabsorption of Na in the kidney results in the reabsorption of water. It follows that inhibition of Na reabsorption will result in diuresis. Because of this, the term diuretic has come to mean any agent that will inhibit the tubular reabsorption of sodium.
Diuretics can be classified by their electrolyte excretion patterns, they possess some combination of:

- **Natriuretic** – enhanced sodium excretion
- **Chloruretic** – enhanced chloride excretion
- **Saluretic** – enhanced sodium chloride excretion
- **Kaliuretic** – enhanced potassium excretion
- **Bicarbonaturetic** – enhanced sodium bicarbonate excretion
- **Calciuretic** – enhanced calcium excretion
Site of diuretic action

- Carbonic anhydrase inhibitors
- Osmotic diuretics
- Loop diuretics
- Thiazide diuretics
- $K^+$-sparing diuretics

SITE 1 DIURETICS
(Work in Proximal Tubule)

Carbonic Anhydrase Inhibitors (CAIs)
The **carbonic anhydrases** form a family of **enzymes** that catalyze the rapid **inter-conversion** of carbon dioxide \((\text{CO}_2)\) and water to bicarbonate \((\text{HCO}_3^-)\) and protons (or vice versa).

**Mechanism of Action of Carbonic Anhydrase Inhibitors (CAIs)**
(H$_2$CO$_3$)

(Inhibitors)
SULFANILAMIDE

- It was introduced for the treatment of bacterial infections, but observed to produce a mild diuresis through inhibition of renal Carbonic Anhydrase (CA).

- It was also found to have severe side effects.

To improve the CA inhibitory property of sulfanilamide, many sulfamoyl-containing (- SO₂NH₂) compounds were synthesized and screened for their diuretic activity and ability to inhibit CA.

Two groups of CA inhibitors emerged:

1. Simple heterocyclic sulfonamides.
HETEROCYCLIC SULFONAMIDES

Sulfanilamide (Lead)

Acetazolamide (Diamox)

Methazolamide (Neptazane)
The prototype is Acetazolamide.

The sulfamoyl group is essential for the production of diuresis.

The sulfamoyl nitrogen atom must remain unsubstituted to retain the activity.

The derivatives with the highest lipid / water partition coefficient and lowest pKa have the greatest CA inhibitory and diuretic activity.
Structure – activity relationships

1. The **sulfamoyl group** is absolutely **essential** for the *in vitro* carbonic anhydrase inhibitory activity.

2. The **sulfamoyl nitrogen** atom must remain **unsubstituted** to both *in vivo* and *in vitro* activities. (This feature explains why all of the antibacterial sulfonamides except *sulfanilamide*, are incapable of inhibiting carbonic anhydrase or exerting a diuresis.)

3. Substitution of a methyl group on one of acetazolamido’s ring nitrogens yields methazolamide, a product that retains carbonic anhydrase inhibitory activity & even more potent.

3. **Sulfamoyl group must be attached** to a moiety that possess aromatic character.
Methazolamide, USP

N-(3-Methyl-5-sulfamoyl-1,3,4-thiadiazol-2(3H)-ylidene)-acetamide

Methazolamide is more potent carbonic anhydrase inhibitor than acetozolamide (the prototype), but is rarely used as diuretic. It is used in treatment of glaucoma, because it displays improved penetration into the eye.
Maximal diuretic activity is observed when this position is substituted with: 
Cl, Br, CF₃ or NO₂

Cl
SO₂NH₂
H₂NO₂S

SO₂NH₂ - unsubstituted sulfamoyl is of paramount importance

Substitution with an amino group increases saluretic, but decreases CA inhibitory activity

Cl
NH₂
H₂NO₂S
SO₂NH₂

SO₂NH₂ - the sulfamoyl moiety can be replaced with a similar electrophilic Group (carbonyl, carbamoyl) that may increase diuretic potency while decreasing CA inhibitory activity

Cl
H₂NO₂S

Chloraminophenamidine

Dichlorophenamidine

( Daranide )
Clinical indications

1. **Glaucoma**: It decreases intraocular pressure by decreasing the rate of aqueous humor formation. **Acetazolamide**: (Diamox), **Methazolamide**: (Neptazane), **Dichlorphenamid**: (Daranide)

2. **Urinary alkalinization**
   - Increases excretion of uric acid (uric acid is relatively insoluble in acidic urine).
   - Acetazolamide will increase renal excretion of weak acids (i.e. aspirin)

3. **Acute mountain sickness**
   - Symptoms: weakness, dizziness, insomnia, headache and nausea.
   - Above 3,000 meters there is increased risk of pulmonary or cerebral edema. Edema can be decreased if acetazolamide is taken 24 hours before ascent.

**Pharmacokinetics**: All CAIs are well absorbed after oral administration. Urine pH increases from $\text{HCO}_3^-$ diuresis within 30 min, maximal at 2 hrs and persist for 12 hours.

**Toxicity**

1. Metabolic acidosis
2. Renal stone formation: Calcium salts are relatively insoluble at alkaline pH.
3. Renal potassium ($\text{K}^+$) wasting due to increased lumen-negative electrical potential
4. Others: Drowsiness, paresthesias, hypersensitive reactions (fever, skin rashes etc.), CAIs may accumulate in patients with renal failure, leading to CNS toxicity.
SITE 2 Diuretics, or LOOP DIURETICS

Works in
Thick Ascending Limb (TAL)
Loop Diuretics: Mechanism of Action

TAL contains **Na\(^+\)/K\(^+\)/2Cl\(^-\) cotransporter** from lumen to TAL cells. Loop diuretic blocks this cotransporter and **increases the excretion of sodium and chloride** by inhibiting their reabsorption in TAL. The diuretic action of this drug is not limited by the development of acidosis, as is the case with CAIs.
Clinical Indications

1. The most important indications include acute pulmonary edema, other edematous conditions, and acute hypercalcemia.

2. Hyperkalemia: Loop diuretics significantly enhance urinary excretion of K+.

3. Acute Renal Failure: Loop diuretics can increase the rate of urine flow and enhance K+ excretion in acute renal failure.

4. Anion Overdose: Loop diuretics are useful in treating toxic ingestion of bromide (Br-), fluoride (F-), and Iodide (I-) which are absorbed in TAL.

Toxicity

1. Hypokalemic Metabolic Alkalosis

2. Ototoxicity

3. Hyperuricemia: Loop diuretics can cause hyperuricemia and gout.

4. Hypomagnesemia

5. Fluid and electrolyte losses

6. Hypersensitivity reactions such as urticaria, fever, and interstitial nephritis.
LOOP DIURETICS

The loop diuretics are of extremely diverse chemical structure such as

1. The organomercurial diuretics

2. The 5-Sulfamoyl-2- and -3-aminobenzoic acid derivatives. For example, furosemide and bumetanide respectively.

3. Phenoxyacetic acid derivatives as ethacrynic acid
1) Organomercurials:

They were the main diuretic therapy from 1926 to the early 1950s.

**Limitations of the organomercurials**

- They cannot be given orally because of poor and erratic absorption.
- After their parenteral administration there is a one- to two-hour lag in the onset of the diuresis.
- Their activity depend on the acid-base status of the individual (i.e., they are ineffective when the urine is alkaline).
- They are cardio- and nephro-toxic.
2) 5-Sulfamoyl-2- and -3-aminobenzoic acid derivatives

**Uses:**

- Edema,
- Hypertension
- **Hypercalciuria** (i.e., an elevated urinary concentration of calcium) are prone to the formation of calcium-containing stones within the urinary tract.
Structure Activity Relationship (SAR)  
5-Sulfamoyl-2- and -3-aminobenzoic acid derivatives

1. The substituent at the 1-position must be acidic. The carboxyl group provides optimal diuretic activity, but other groups, as tetrazole, may have respectable diuretic activity.

2. A sulfamoyl group in the 5-position is essential for optimal high-ceiling diuretic activity.

3. The activating group (x-) in the 4-position can be Cl- or CF₃-, a phenoxy-, alkoxy-, anilino-, benzyl-, or benzoyl- group
SAR of 5-Sulfamoyl-2- and -3-aminobenzoic acid derivatives:

Major differences between the two series of 5-sulfamoyl-benzoic acids is based in the nature of the functional groups that can be substituted into the 2-and 3-positions with the retention of maximal diuretic activity:

i. **Substituents** that can be tolerated at the 2-amino group of the 5-sulfamoyl-2-aminobenzoic acid series are extremely limited, and no deviations are allowed on the few moieties that are acceptable. For example, only furfural-, benzyl-, and thienylmethyl (in decreasing order) yield derivatives with maximal diuretic activity.

ii. **Substituents at the 3-amino group** of the 5-sulfamoyl-3-aminobenzoic acid can very widely without affecting optimal diuretic activity.
The substituents that can be tolerated on the 2-amino group are limited and no deviation are allowed on the few moieties that are acceptable.

Only furfuryl, benzyl and thienylmethyl yield derivatives of diuretic activity.

\[ R = \text{furfuryl} \quad > \quad \text{benzyl} \quad > \quad \text{thienylmethyl} \]

Furosemide (Lasix)  Azosemide
5-SULFAMOYL-3-AMINOBENZOIC ACID

R = A wide variety of alkyl groups

Bumetanide (Bumex)

Piretanide
Synthesis of Furosemide

1) ClSO₃H

2) NH₃

Furfurylamine

Δ, 130 °C
Phenoxyacetic acids
Ethacrynic Acid, (Edecrin)

2,3-Dichloro-4-(2-methylene-1-oxobutyl)phenoxyacetic acid

Uses:
1. Same uses as cited for furosemide and bumetanide.
2. Ethacrynic acid is prescribed for individual who has a known hypersensitivity to Sulfamoyl containing drugs.

Adverse Effects:
1. Same adverse effects as noted with Furosemide and bumetanide except those related to sulfamoyl group.
2. Ototoxicity and GIT effects (GIT hemorrhage) more than furosemide and bumetanide.
Pharmacokinetics

- Ethacrynic acid alkylate the thiol endogenous compounds such as glutathione (RSH = glutathione) to give the sulfhydryl-containing conjugates, this conjugate is converted to the ethacrynic acid-cysteine and ethacrynic acid-N-acetyl cysteine conjugates.

- Ethacrynic acid-cysteine conjugate is unstable in vitro and in vivo that release ethacrynic acid, cysteine.

Ethacrynic acid, ethacrynic acid glutathione, ethacrynic acid-cysteine are equiefficacious diuretics.
Site 3 Diuretics
Thiazide and Thiazide-like Diuretics
Works in
Distal Convoluted Tubule
Site 3 Diuretics: Thiazide and Thiazide-like Diuretics

Thiazides and related diuretics inhibit the reabsorption of sodium and chloride ions in the ascending THIN portion of the loop of Henle and the early distal convoluted tubule of the nephron. This action results in the excretion of sodium, chloride, and water.
**Uses:**

Treatment of hypertension, edema CHF, hepatic cirrhosis, corticosteroid and estrogen therapy, and renal dysfunction.

**Adverse effects:**

1. Hypersensitivity reactions, Cross-hypersensitivity may also occur between thiazides and sulfamoyl-containing diuretics.
2. Hypokalemia
3. A slight reduction in the cardiac output, plasma volume and blood pressure.
4. Increase in the proximal tubule reabsorption of luminal fluid and solutes due to the reduction in plasma volume.
5. Hypercalcemia or hyperuricemia.
6. Reduction in the glomerular filtration rate.
7. Hyperglycemia
Structure-Activity Relationships: Thiazide Diuretics

1. The 2-position can tolerate small alkyl groups as CH₃.
2. Substitutents at the 3-position determine the potency and duration of action of the thiazides.
3. Saturation of C-C bond between the 3 and 4 positions of the benzothiadiazine-1,1-dioxide nucleus increases the potency of this class of diuretics approximately 3-10 fold.
4. Direct substitution of the 4-, 5-, or 8-position with an alkyl group usually results in diminished diuretic activity.
5. Substitution of the 6-position with an activating group is essential for diuretic activity. The best substituent include Cl-, Br-, CF₃-, and NO₂-groups.
6. The sulfamoyl group in the 7-position is essential for diuretic activity.
Examples of Thiazide Diuretics

- **Chlorothiazide**: 6-Chloro-2H-1, 2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
- **Benzthiazide (Hydrex)**: 6-Chloro-3-[(phenylmethyl) thio]methyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
- **Hydrochlorothiazide, (Esidrix)**: 6-Chloro-3, 4-dihydro-2H-1, 2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide
- **Bendroflumethiazide**: 3-Benzyl-3,4-dihydro-6 (trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1, 1-dioxide
Synthesis of Thiazides

3-chlorobenzenamine + sulfurochloridic acid → 4-amino-6-chlorobenzene-1,3-disulfonyl dichloride

H₂N₂S₄O₂NH₂ → H₂N₂S₄O₂NH₂

H₂N₂S₄O₂NH₂ → H₂O

H₂N₂S₄O₂NH₂ → H₂O

H₂N₂S₄O₂NH₂ → H₂O

H₂N₂S₄O₂NH₂ → H₂O
The sulfamoyl group para to the activating group of thiazides could be replaced by several other electronegative groups (X-) with retention of diuretic activity (as R = amide, carbonyl, carboxyl groups, etc) in the meta-disulfamoylbenzene.

These diuretics known as thiazide-like diuretics.

Their site of action, efficacy, electrolyte excretion pattern, and adverse effects resemble the thiazides.
**Chlorthalidone (Hygroton):** 2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyI)benzenesulfonamide

**Synthesis**

2-(3-amino-4-chlorobenzoyl)benzoic acid

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2\text{N} & \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{H} \\
\text{H}_2\text{N} & \quad \text{O} & \quad \text{C} \quad \text{O} \quad \text{H} \\
\end{align*}
\]

\[\xrightarrow{1) \text{HNO}_2} \]

2-(3-amino-4-chlorobenzoyl)benzoic acid

\[
\begin{align*}
\text{Cl} & \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{H} \\
\text{Cl} & \quad \text{O} & \quad \text{C} \quad \text{O} \quad \text{H} \\
\end{align*}
\]

\[\xrightarrow{2) \text{SO}_2, \text{CuCl}_2} \]

2-(4-chloro-3-(chlorosulfonyl)benzoyl)benzoic acid

\[
\begin{align*}
\text{Cl} & \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{H} \\
\text{Cl} & \quad \text{O} & \quad \text{C} \quad \text{O} \quad \text{H} \\
\end{align*}
\]

\[\xrightarrow{\text{SOCl}_2} \]

2-chloro-5-(1-chloro-3-oxo-1,3-dihydroisobenzofuran-1-yl)benzene-1-sulfonyl chloride

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2\text{NO}_2\text{S} & \quad \text{H} \quad \text{N} \quad \text{O} \\
\text{Cl} & \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{H} \\
\end{align*}
\]

\[\xrightarrow{\text{NH}_3} \]

Chlorthalidone (Hygroton)

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2\text{NO}_2\text{S} & \quad \text{H} \quad \text{N} \quad \text{O} \\
\text{Cl} & \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{H} \\
\end{align*}
\]
Site 4 Diuretics: Potassium-sparing diuretics

Works in Distal Convoluted Tubules
Diuretics that increase sodium and chloride excretion, without a concomitant increase in the urinary excretion rate of potassium. These agents are known as potassium-sparing (or potassium-saving) diuretics or anti-kaliuretic agents. They work in the distal convoluted tubules of the kidney.

Classification:
1. Aldosterone antagonists (e.g. Spironolactone)
2. Direct-acting diuretics (e.g. triamterene and amiloride)

Properties and uses:
- These agents are not potent diuretics when used alone but, when combined with a thiazide - eg, Aldactizide.
- They reduce potassium loss, increase sodium excretion.
- Minimize alkalosis.
- The onset of diuresis with combination therapy is much more rapid than with spironolactone alone.
Aldosterone antagonists:
Aldosterone, a hormone produced by the adrenal cortex, **enhances the reabsorption of sodium in the distal convoluted tubules of the kidney.**

**Spironolactone (Aldactone) antagonizes the action of aldosterone.**
When this activity of aldosterone is blocked, sodium (but not potassium) and water are excreted.

**Uses**
- Treatment of edema
- Antihypertensive agent.
- Primary use is in combination with diuretics that act at site 2 or 3 to reduce the hypokalemic effect of the latter groups of diuretics.

**Adverse Effects**
- **Hyperkalemia**
- Metabolic acidosis.
- **Gynecomastia in men** and Breast tenderness and menstrual disturbances in women because of its residual hormonal activity.
- Minor GIT symptoms.

**Spironolactone (Aldactone):**
7α-(Acetylthio)-17β-hydroxy-3-oxopregn-4-ene-21-carboxylic acid γ-lactone
Metabolism:

Spironolactone is metabolized to Canrenone which is an active aldosterone antagonist.

Synthesis
**Triamterene: 2,4,7-triamino-6-arylpteridines**

**SAR:**
- Para-substitution of phenyl ring with (-OH group) increases activity
- The phenyl group can be replaced by small heterocyclic rings
- The **amino groups must be un-substituted.**
- It has a structural similarity to folic acid and certain dihydrofolate reductase inhibitors, but it has little, if any, of their activities.

**Uses:**
- Treatment of edema, hypertension.
- Used in combination with other diuretics that act at site 2 or 3 to prevent hypokalemia.

**Adverse Effects:**
- Hyperkalemia, renal stones formation, GIT symptoms.
**Pyrazinoylguanidines**

**Mechanism of Action:**
“Plugs” the sodium channels preventing electrogenic reabsorption of 2-3% of the filtered Na⁺.

*Directly* blocks Na⁺ entry through sodium-selective ion channels, which directly alters the Na+/K+ exchange mechanism in the distal nephron.

**SAR:**
- Optimal diuretic activity is observed when
  1. The 6 position is substituted with chlorine.
  2. The amino group at 3, 5 position are unsubstituted.
  3. The guanidino nitrogen are not substituted with alkyl group.

**Amiloride Hydrochloride** (Midamor, Moduretic)

Uses and Adverse effects as triametrine

- Moderately plasma protein bound, oral bioavailability 15-20%,
- Used in combination with hydrochlorthiazide (Moduretic®).
- **Side effects:** hyperkalemia, nausea, vomiting, headache, diarrhea
Osmotic diuretics

Osmotic diuretics increase the density of the filtrate in the glomerulus. This prevents selective reabsorption of water, which allows the water to be excreted. Sodium and chloride excretion is also increased.

They have the following key features:
1. They are passively filtered by glomerular filtration.
2. They undergo limited reabsorption in the renal tubules
3. They are metabolically and pharmacologically inert,
4. They have a high degree of water solubility

Examples, Mannitol, Theophylline
The prototypic osmotic diuretic, D-Mannitol is a water-soluble, lipid-insoluble hexahydroxy alcohol. It does not diffuse GIT or renal tubule epithelium. Mannitol should be given by the **intravenous (IV) route**.

Mannitol enters renal luminal fluid only by glomerular filtration. Its **high luminal fluid concentration creates an osmotic effect that may prevent the reabsorption of up to 28% of the filtered load of water**.

Mannitol may be employed prophylactically to avoid acute renal failure or the reduction of CSF volume and pressure.

Because solutions of mannitol may expand the extracellular fluid volume, they should not be used in patients with severe renal disease or cardiac decompensation.
The prototypic xanthine, is known to promote a **weak diuresis** by stimulation of cardiac function and by a direct action on the nephron. Although theophylline is **infrequently used as a diuretic**, a diuresis may be an observed side effect when it is used as a bronchodilator.
Summary of Diuretics

Diuretics
1. Acetazolamide
2. Osmotic agents (mannitol)
3. Loop agents (e.g., furosemide)
4. Thiazides
5. Aldosterone antagonists
6. ADH antagonists
Medicinal Chemistry III
(Course code: 0510411)
First Examination
B Pharm, Semester – 1, 2016/2017

Date: Tuesday, 22/11/2016
Time: 50 min (3.00 pm to 3.50 pm)
Student Name: Abdulla Mohammad Nsour
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Total Marks: 20
Section: 02
Class Roll No.: 01
Thank You