Diuretics
Dr S Mathijs
Department of Pharmacology

What is a diuretic?
• Drug inducing state of increased urine flow
• Ion transport inhibitors, decrease reabsorption of sodium at different sites in the nephron
• Sodium and other ions such as chloride enter the urine in greater amounts than normal along with water, which is carried passively to maintain osmotic equilibrium

Classification

<table>
<thead>
<tr>
<th>Name</th>
<th>Example</th>
<th>Site of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonic anhydrase inhibitors (CAI)</td>
<td>Acetazolamide</td>
<td>Proximal convoluted tubule</td>
</tr>
<tr>
<td>Osmotic diuretics</td>
<td>Mannitol, Isosorbide, Urea</td>
<td>Proximal convoluted tubule</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Furosemide, Bumetanide, Torasemide</td>
<td>Ascending loop of Henle</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Hydrochlorothiazide, Indapamide, Chlorthalidone</td>
<td>Distal convoluted tubule</td>
</tr>
<tr>
<td>K⁺ sparing diuretics</td>
<td>Spironolactone, Amiloride, Triamterene</td>
<td>Collecting duct</td>
</tr>
</tbody>
</table>

High vs low ceiling diuretics

Loop diuretics
• Eg Furosemide, Bumetanide, Torasemide
• Act on thick segment of ascending Loop of Henle
• Inhibit the transport of NaCl out of tubule into interstitial tissue by inhibiting Na⁺/K⁺/2Cl⁻ carrier in the luminal membrane
• Direct inhibiting effect on carrier – act on Cl⁻ binding site
• More solute is delivered to distal portion of nephron where its osmotic pressure further reduces water reabsorption
### Loop diuretics: other actions
- Increased excretion of Ca²⁺ and Mg²⁺
- Decreased excretion of uric acid
- Have venodilator action: drop in blood pressure

### Kinetics
- Absorbed from GIT
- IV
- Plasma protein bound – does not pass into glomerular filtrate
- Secreted in proximal convoluted tubule by organic acid transport mechanism
- Excreted into urine
- Fraction metabolized in liver
- Peak within 30 min if given IV
- Duration of action 3-6 hours

### Side effects (SE)
- Hypokalaemia
- Metabolic alkalosis
- Hypotension
- Thromboemboli
- Allergic reaction
- Gout
- Deafness

### Uses
- Pulmonary oedema
- Heart failure
- Cirrhosis
- Nephrotic syndrome
- Renal failure
- HT
- Hypercalcaemia
- Elimination of drugs during poisoning

### Drug interactions
- **Aminoglycosides**: enhances ototoxicity, and nephrotoxicity

### Thiazides
- **Eg. Hydrochlorothiazide, Cyclopenthiazide**
- Reduces active reabsorption of Na⁺ and Cl⁻ by binding to Cl⁻ side of electroneutral NaCl co-transport system and inhibits its action
- K⁺ loss is significant
- Excretion of uric acid ↓
- Mg²⁺ excretion ↑
- Hypochloremic alkalosis can occur
- Vasodilatation
- Hyperglycaemia (inhibit Insulin secretion)
- Tolerance does not develop
- Body PH does not affect their action
Uses

- HT – (blood volume reduced, later direct effect on blood vessels)
- Mild heart failure
- Severe resistant oedema
- Nephrogenic diabetes insipidus (antidiuretic effect)
- Pt who form calcium kidney stones
- Nephrotic syndrome
- Liver cirrhosis

SE

- Hyperglycaemia
- ↑ Plasma cholesterol, triglycerides, LDL, VLDL
- Male impotence (reversible)
- Gout
- Hypokalaemia
- Hypersensitivity reaction (sulphonamide derivative)

Rare SE

- Skin rash
- Parasthesia
- Weakness/tiredness
- Bone marrow depression
- Pancreatitis

Drug interactions

- NSAIDs: reduced diuretic efficacy
- Beta blockers: potentiate hyperglycaemia/hyperlipidaemia
- Steroids: enhance hypokalaemia
- Hypokalaemia potentiates digitalis toxicity
- Lithium: diuretics increase reabsorption of lithium in proximal convoluted tubule

Spironolactone

- Competitive antagonist of Aldosterone
- Inhibit Na⁺ retaining action of aldosterone
- ↓ K⁺ and ↓ H⁺ secretion

Uses

- Severe heart failure
- Resistant hypertension
- Combination with thiazides/loop diuretics to prevent potassium loss
- Primary hyperaldosteronism (Conn’s syndrome)
- Secondary hyperaldosteronism
- Cirrhosis/ascites
- Nephrotic syndrome
- Chronic diarrhea
### Side effects
- GIT disturbances
- Hyperkalaemia
- Metabolic acidosis
- Gynaecomastia
- Menstrual disturbances
- Testicular atrophy
- Peptic ulcers

### Eplerenone
- New aldosterone antagonist
- No oestrogenic effects of Spironolactone
- Hypertension
- Post myocardial infarction with impaired left ventricle function

### Amiloride/Triamterene
- Inhibit Na⁺ reabsorption and reduce K⁺ secretion in collecting tubules/ducts
- Block luminal Na⁺ channels by which Aldosterone produces main effect
- Promotes excretion of uric acid
- K⁺ sparing ability
- Co-amiloside: Amiloride/HCTZ

### SE
- Metabolic acidosis
- Hyperkalaemia
- GIT disturbances
- **Triamterene**: folic acid deficiency – avoid in pregnancy

### Drug interactions
- K⁺ sparing diuretics and ACE inhibitors: potentiate hyperkalaemia

### Osmotic diuretics
- Mannitol, Isosorbide, urea, glucose
- Osmotically active molecule filtered by glomeruli but not absorbed by tubules
- Draw water osmotically with them and reduce concentrating ability of kidney, as concentration gradient of Na⁺ from the tubular fluid to the cells is smaller
Uses
- Prophylaxis against ATN in shock and hepatorenal syndrome. Protects kidney by maintaining adequate flow of diluted urine
- Acute poisoning
- ↑ICP
- ↑IOP
- Initiate diuresis in pt with chronic dilutional hyponatraemia

SE
- Expansion of extracellular fluid volume
- Hyponatraemia
- N+V
- Headache

CAI
- Hydrogen ions that are formed are exchanged for sodium
- Diffusible carbon dioxide taken up by the tubular cells to form bicarbonate again
- CAI prevent formation of hydrogen ions
  1. H⁺ accumulate – metabolic acidosis
  2. Na⁺ and K⁺ lost with water in urine
  3. Urine alkaline due to lack of H⁺

Uses
- Glaucoma – production of aqueous humor is reduced
- Alkalinize urine in treatment of poisoning with weak acids such as salicylates
- Prophylaxis against mountain sickness – metabolic acidosis enhances hyperventilation and respiratory alkalosis which occurs during acclimatization, develops more quickly. Hyperventilation increases the arterial oxygen saturation and reduces tissue hypoxia.

Sodium and water
- Sodium disorders are disorders of both sodium and water
- Dysregulation of water balance usually primary abnormality
- Water moves freely between body fluid compartments
- Sodium is extracellular cation
- Sodium critical for maintenance of ECF
Causes of hyponatremia

- Drug induced hyponatremia
  - Diuretics
  - ACE inhibitors
  - PPI
  - Carbamazepine
  - NSAIDs
  - Antipsychotics
  - Antidepressants
  - Trimethoprim-sulphamethoxazole

Treatment of hyponatremia

- How urgent?
- Chronicity
- Cause of hyponatremia
Vasopressin

- ADH = antidiuretic hormone
- Water/sodium balance
- Thirst: stimulated by increase in osmolality or decrease in blood pressure or pressure
- Water excretion regulated by vasopressin:
  \[ \text{↑ in osmolality} = \text{↑ ADH} = \text{↑ water reabsorption} \]

Vasopressin antagonists

Causes of hypernatraemia
Drug induced hypernatraemia

- Loop diuretics
- Mannitol
- Amphotericin B
- Demeclocycline
- Lithium
- Lactulose

Hypernatraemia

- Serum sodium > 145 mmol/L
- Associated with high mortality (40-75%)
- Loss of total body free water or gain in total body sodium
- Establish volume and hydration status
- Measure urine volume, renal function, calcium, potassium and glucose
- Urine/serum osmolality

Treatment of hypernatraemia

- Acute: compensatory neuronal changes have not occurred, correct rapidly
- Chronic hypernatraemia: neuronal oedema, correct cautiously
- Maximum rate: 1 mmol/L/hour with total maximum decrease of 10 mmol/L in 24 hours
- Correct hypovolaemia with colloid or sodium chloride 0.9%, thereafter give hypotonic fluid (glucose 5% or half strength sodium chloride)
- Calculate total water deficit
- Hypervolaemic hypernatraemia: salt restriction, diuretics
- Diabetes insipidus: desmopressin

Diabetes insipidus

- Desmopressin
  - Synthetic analogue of vasopressin
  - Longer acting, minimal vasoconstrictor effect
  - Factor VIII releasing activity from endothelial cells
  - Diagnosis and treatment of diabetes insipidus
  - Oral, intranasal or IVI
  - Sodium and fluid balance must be assessed frequently
  - CI: CVS and renal impairment

Potassium

- Intracellular cation
- 55% of filtered potassium is reabsorbed in proximal tubule
- 10% of filtered potassium reaches the distal tubule, this segment provides regulation of potassium excretion
Hypokalaemia
- Uncommon in normal subjects
- Drug use/diet/pathology

Treatment of hypokalaemia
- IVI potassium if hypokalaemic emergency
- Give peripherally at rate up to 10 mmol/hour
- Oral as potassium chloride or potassium citrate

Hyperkalaemia
- Common in renal disease
- Drug use

Drug causes of reduced potassium excretion
- ACE inhibitors
- ARB
- Beta blockers
- Spironolactone
- NSAIDs
- Potassium sparing diuretics
- Calcineurin inhibitors: tacrolimus and cyclosporin

Treatment of hyperkalaemia
- Stop all drugs
- Cardiac stabilization
- Redistribute potassium into intracellular fluid
- Lower total body potassium

Calcium
- Critical component of bone and mineralized structures
- Intracellular cation
- Effects regulated by calmodulin
- Plasma calcium ionized or protein bound
- Calcium balance determined by gut absorption and renal excretion, bony skeleton providing reserve pool of calcium
- Parathyroid hormone secretion is modified according to calcium levels
Hypercalcaemia

- Malignancy most common cause, followed by hyperparathyroidism
- "Moans, groans, stones and bones"

Treatment of hypercalcaemia

- Treat underlying cause
- Volume expansion with sodium chloride 0.9%
- IVI furosemide
- Monitor electrolytes and fluid status
- Bisphosphonates: inhibit bone resorption

Hypocalcaemia

- Neuromuscular dysfunction
- Bronchospasm and laryngospasm
- Chvostek sign
- Trousseau sign

Treatment of hypocalcaemia

- Symptomatic: IVI calcium gluconate
- Oral calcium and vitamin D
Phosphate

- Essential component of bone and soft tissues
- Kidneys maintain total body phosphate balance
- Freely filtered
- Proximal tubular reabsorption
- Renal excretion influenced by PTH, calcitriol, diet, fibroblast growth factors 23 and 7, and klotho gene

Hypophosphataemia

- Common in alcoholics and acute sepsis
- Part of malabsorption syndrome
- Phosphate binding agents
- Hyperparathyroidism
- Post renal transplant
- Renal Fanconi syndrome
- Drug toxicity: Cisplatin, tenofovir

**Treatment of hypophosphataemia**

- IVI phosphate in critical patients
- Monitor for metastatic calcification or hypocalcaemia

**Hyperphosphataemia**

- Treat underlying cause
- Volume expansion and diuresis with saline
- Furosemide
- Haemodialysis or haemofiltration
- Diet restriction
- Oral phosphate binders with meals: sevelamer and lanthanum

**Magnesium**

- Critical for cellular and metabolic processes
- Intracellular cation
- Balance of gut absorption and renal excretion maintains plasma magnesium
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<td>• Up to 10% of hospitalized patients</td>
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<tr>
<td>• Common in alcoholics</td>
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<tr>
<td>• Malabsorption syndrome</td>
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<tr>
<td>• PPI</td>
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<tr>
<td>• Excessive laxative use</td>
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<tbody>
<tr>
<td>• IVI magnesium sulphate</td>
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<tr>
<td>• Oral magnesium salts</td>
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<tr>
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<td>• Antacids and laxatives</td>
</tr>
<tr>
<td>• Lithium</td>
</tr>
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<td>• Hypothyroidism</td>
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<td>• Stop magnesium therapy</td>
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