Pharmacology of volume regulation

Water accounts for 50% - 60% of total body weight. Changes in total body water is reflected by changes in body weight. Approx 2/3 is intracellular fluid (ICF) the remainder is extracellular fluid (ECF) comprising the interstitial fluid and the vascular compartment.

All compartments have the same osmolality (280 – 290 mosmol/kg). The major intracellular solute is potassium whilst the major extracellular solute is sodium chloride. The major determinant of plasma osmolality is sodium concentration.

Plasma osmolality is approximated as:

\[ P \text{ (osm)} = [Na^+] \times 2 + [\text{urea}] + [\text{glucose}] \text{ mosmol/kg} \]
Body water homeostasis is effected by thirst and the urine concentrating and diluting functions of the kidney. These in turn are controlled by intracellular osmoreceptors, principally in the hypothalamus, to some extent by volume receptors in capacitance vessels and via the renin angiotensin system.

An increase in intracellular osmolality e.g. after water deprivation, stimulates both thirst and release of anti-diuretic hormone (ADH) from the posterior pituitary. Thirst stimulates increased water intake while ADH increases the reabsorption of water from the tubular fluid by its action on the distal tubules of the kidney.
Increased extracellular volume occurs in a number of disease states. The physical signs depend on the distribution of excess volume. Peripheral oedema is caused by expansion of extracellular volume by at least 2 litres (15%). The ankles are frequently the first part of the body to be affected.

Oedema may also be noted in the face and in the sacral area. Expansion of the interstitial volume may also cause pulmonary oedema, pleural effusion, pericardial effusion and ascites.
Extracellular volume expansion is due to sodium chloride retention and many of the underlying causes are associated with renal sodium chloride retention, these include:

**Heart failure** – increased venous pressure causing oedema formation, activation of the renin angiotensin system (RAS) and increased activity of the autonomic nervous system (ANS).

**Hypoalbuminaemia** - loss of plasma oncotic pressure leading to loss of water from the vascular space to the interstitial space, activation of RAS.

**Hepatic cirrhosis** – complex mechanism involving peripheral vasodilation, activation of RAS causing sodium retention.

**Renal impairment** – decreased GFR decreasing capacity to excrete sodium.
Diuretics

Treatment of conditions such as heart failure invariably results in the administration of diuretic drugs. Diuretics account for over 3.2% of all prescription items under the GMS scheme.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prescribing frequency (% GMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>579,164 (1.3%)</td>
</tr>
<tr>
<td>Furosemide + K</td>
<td>227,387 (0.5%)</td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td>409,745 (0.92%)</td>
</tr>
<tr>
<td>Bendroflumethiazide + K</td>
<td>240,820 (0.5%)</td>
</tr>
</tbody>
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Diuretics

There are a number of different drug classes which are used as diuretic agents, these include:

- Carbonic anhydrase inhibitors
- Loop diuretics
- Thiazide and thiazide-like diuretics
- Potassium sparing diuretics
- Osmotic diuretics
Carbonic anhydrase inhibitors

Carbonic anhydrase plays a key role in NaHCO3 reabsorption. Isotonic reabsorption of water follows. Inhibition of CA may result in the loss of 35% of filtered load of HCO3.

The fractional excretion of Na+ may be as much as 5%, for K+ could be as much as 70%
Acetazolamide, a sulphonamide derivative, is the prototype of a class of agents that have a limited role as diuretics. It inhibits the enzyme carbonic anhydrase. The diuretic actions are self-limiting due to the resulting metabolic acidosis which decreases the filtered load of $\text{HCO}_3^-$.
Carbonic anhydrase inhibitors

Acetazolamide has high oral bioavailability (> 95%) and has a half-life of 6 – 9 hours. Its main route of elimination is renal. As carbonic anhydrase is present in a number of extrarenal tissues including the eye, gastric mucosa, pancreas, CNS and erythrocytes acetazolamide has a number of additional therapeutic applications.

- Open-angle glaucoma. Inhibition of CA decreases the rate of formation of aqueous humor and reduces intraocular pressure
- Epilepsy. Sometimes effective in the treatment of absence seizures its usefulness is limited by the rapid development of tolerance.
- Altitude sickness. It is more appropriately used as a prophylactic therapy.
- Familial periodic paralysis.

Adverse effects of acetazolamide include some characteristic sulphonamide effects:
- bone marrow suppression, skin rashes, nephrotoxicity, allergic reactions
- somnolence, paraesthesiae
- renal calculi (precipitation of Ca+ phosphate stones in alkaline urine)
- worsening of metabolic or respiratory acidosis (e.g. severe COPD).
Loop diuretics

The mechanism of action of the loop diuretics is through inhibition of the Na/K/2Cl cotransporter in the luminal membrane of the ascending loop of Henle.

Loop diuretics
- Furosemide
- Bumetanide
- Piretanide

As a result of the reduction in Na and Cl absorption at the ascending loop of Henle loop diuretics (a) reduce the tonicity of the medullary interstitium and (b) inhibit reabsorption of water in the collecting duct.
Loop diuretics

In addition to the diuretic effect loop diuretics have vasodilator properties which reduces left ventricular filling.

Clinical uses of loop diuretics include:

- Acute pulmonary oedema
- Hypertension
- Acute renal failure
- Oedema e.g. ascites, nephrotic syndrome

Recognised adverse effects of loop diuretics

- Hypokalaemia, hyponatraemia, hypovolaemia +/- hypotension
- Hypocalcaemia, hypomagnesemia, hyperuricaemia, alkalosis,
- Ototoxicity (hearing loss, tinnitus)
Thiazide diuretics

The mechanism of action of the thiazide diuretics is through inhibition of the Na/Cl transporter in the basolateral membrane of the distal tubule.

Thiazides produce a moderate diuresis as a maximum of 5% of the filtered Na load is excreted.

Calcium reabsorption is enhanced by stimulation of the Na/Ca countertransport system.

Thiazide diuretics
Bendroflumethiazide
Hydrochlorothiazide
Metolazone
Chlorthalidone
Thiazide diuretics

Clinical uses of thiazide diuretics include:
- Hypertension
- Oedema e.g. ascites, nephrotic syndrome, congestive cardiac failure

Recognised adverse effects of thiazide diuretics
- Hypokalaemia
- Hyponatraemia
- Hypercalcaemia
- Hyperglycaemia
- Hyperuricaemia
- Hypomagnesemia
- Alkalosis
- Erectile dysfunction
Thiazide diuretics

Efficacy & toxicity versus dose

Adverse effects

Anti hypertensive effect

1.25 mg  2.5 mg  5.0 mg

Bendroflumethiazide (daily dose)
Potassium sparing diuretics increase the excretion of sodium at the distal tubule and the collecting ducts. There are two groups (a) sodium channel blockers and (b) aldosterone antagonists.

**Na channel blockers**
- Amiloride
- Triamterene

**Clinical indications**
- Hypertension & oedema

**Aldosterone antagonists**
- Spironolactone
- Eplerenone

**Clinical indications**
- Hypertension & heart failure


Potassium sparing diuretics

Recognised adverse effects of potassium sparing diuretics

- Hyperkalaemia
- Metabolic acidosis
- Gastrointestinal upset

Spironolactone binds to other steroid receptors resulting in

- Gynaecomastia
- Menstrual disorders
- Hirsutism
- Impotence
Osmotic diuretics

Osmotic diuretics undergo glomerular filtration but are very poorly absorbed from renal tubular fluid. Their main diuretic action is exerted at the proximal tubule reducing Na and water reabsorption.

An example of an osmotic diuretic is mannitol. An infusion of mannitol will increase the plasma volume which makes it unsuitable for the treatment of most causes of oedema including cardiac failure.

As osmotic diuretics do not enter cells or some anatomical areas e.g. brain, when they are administered as a concentrated solution water leaves cells down the osmotic gradient. Therefore mannitol will reduce intracranial pressure and is used in the treatment of cerebral oedema.
Disorders of sodium concentration

These are best thought of as disorders of body water content as sodium content is regulated by volume receptors. Water content is adjusted to maintain a normal osmolality and a normal sodium concentration. Disturbances of sodium concentration are caused by disturbances of water balance.

**Hyponatraemia**

Hyponatraemia (Na+ < 130 mmol/l) is one of the commonest biochemical abnormalities. It may be associated with normal, decreased or increased extracellular volume and total body sodium content.

**Hyponatraemia with normal extracellular volume**

- Abnormal ADH release: deficiency of ACTH or glucocorticoids, hypothyroidism, K+ depletion
- Stress: surgery
- ADH like substances: Oxytocin
- Substances stimulating ADH release: glucose, alcohol
- Increased sensitivity to ADH: Chlorpropamide, tolbutamide
- Syndrome of inappropriate ADH
Disorders of sodium concentration

**Hyponatraemia**

Hyponatraemia with decreased extracellular volume

- Gastrointestinal: Vomiting, diarrhoea, haemorrhage

Hyponatraemia with increased extracellular volume

- Heart failure
- Liver failure
- Oliguric renal failure
- Hypoalbuminaemia
Symptoms will depend on the rate of fall and/or the level of hyponatraemia and include: anorexia, nausea, vomiting, restlessness, irritability, confusion, coma, convulsions

Causes of SIADH include:

- Tumours: small cell carcinoma of the lung, lymphoma, prostate etc
- Pulmonary lesions: pneumonia, tuberculosis, lung abscess
- CNS causes: meningitis, subdural, tumour, head injury, abscess
- Metabolic causes: alcohol withdrawal, porphyria
- Drugs – carbamazepine
  - fluoxetine, paroxetine, citalopram, sertraline ( > 2.5 % of GMS presc )
  - imipramine, clomipramine, dothiepin
  - morphine
  - haloperidol, olanzapine, rispiridone ( > 0.6 % of GMS prescriptions )
  - cyclophosphamide, vincristine
Demeclocycline inhibits adenylate cyclase and renders the collecting ducts insensitive to antidiuretic hormone (ADH, vasopressin). It has been used to treat SIADH.

In common with other tetracyclines, demeclocycline increases plasma urea and can produce deterioration in renal function.

Vasopressin (ADH) renders the collecting ducts permeable to water.

Demeclocycline inhibits the effect of ADH.
Hypernatraemia

Hypernatraemia is much rarer than hyponatraemia and usually indicates a water deficit, causes include:

- Pituitary or ‘central’ diabetes insipidus (failure of ADH secretion) secondary to neurosurgery, head injury, sarcoidosis, etc
- Nephrogenic diabetes insipidus or ‘drug induced’ DI (failure of response to ADH). Drugs producing DI include:
  - lithium
  - tetracyclines
  - amphotericin
  - primidone

Polydipsia and polyuria in central diabetes insipidus van be prevented by vasopressin. Currently the stable analogue desmopressin is used via the nasal mucosa. It is ineffective for nephrogenic diabetes insipidus where paradoxically thiazide diuretics reduce polyuria