Diuretics are commonly prescribed medicines used to treat oedema caused by conditions such as heart failure, liver cirrhosis and kidney disease. Some diuretics may be used to treat hypertension. However, adverse effects are common and it has been estimated that diuretics contribute to around one in five of all medicines-related hospital admissions.

Diuretics work by increasing the excretion of sodium from the kidneys, drawing water along with the sodium. Around 180 litres (l) of water is filtered by the kidneys each day, but only around 1.5 l of this will actually leave the body.

Filtration occurs in the nephrons of the kidney, when blood passes through the glomerular capillaries at high pressure. Water and sodium are forced out of the blood and into the renal tubule at Bowman's capsule (see ‘Diuretic sites of action’, page 88). The filtrate contains other small molecules, such as potassium and chloride ions, and glucose. Larger structures, such as red blood cells and large proteins, remain in the blood.

**SUMMARY BOX**

In this article you will learn:

- The site of action for commonly used diuretics
- How different classes of diuretics affect water reabsorption in the kidneys
- The common side effects of different diuretic classes

Light micrograph of kidney collecting ducts, which along with the distal convoluted tubule is the site of action for potassium-sparing diuretics
Reabsorption occurs as sodium and water pass through the different sections of the renal tubule. Sodium is reabsorbed via active transport and passive diffusion, whereas water is reabsorbed through osmosis, moving from areas of low electrolyte concentration to areas of high electrolyte concentration, i.e. from the renal tubule to the blood.

**Carbonic anhydrase inhibitors**

Acetazolamide is the only oral carbonic anhydrase inhibitor used in practice. It decreases the amount of sodium that is reabsorbed from the proximal convoluted tubule, increasing the volume of water excreted in the urine.

Carbonic anhydrase catalyses the formation of carbonic acid from water and carbon dioxide in tubular cells. Carbonic acid then dissociates into bicarbonate ions (which are reabsorbed into the blood) and hydrogen ions, which are exchanged for sodium ions into the lumen of the tubule. Reversible inhibition of carbonic anhydrase results in reduced sodium and hydrogen ion exchange and thus increases excretion of sodium, bicarbonate and water.

Acetazolamide is considered a weak diuretic because excess sodium delivered from the proximal tubule can be reabsorbed further along the renal tubule.

The loss of bicarbonate in the kidney can cause metabolic acidosis, which can be useful when acetazolamide is used in combination with a loop diuretic to prevent metabolic alkalosis (see below).

Acetazolamide is not commonly used as a diuretic, and is mainly prescribed for glaucoma to reduce intraocular pressure by suppressing the secretion of bicarbonate and water into the aqueous humour. It is also used unlicensed as prophylaxis for altitude sickness.

**Loop diuretics**

The main site of sodium reabsorption is in the thick ascending limb of the loop of Henle. Here, sodium ions are actively transported out of the tubule by the membrane transport protein sodium-potassium-chloride (Na+/K+/2Cl-) cotransporter. Loop diuretics (e.g. furosemide, bumetanide and torasemide) compete with chloride ions on this transporter to inhibit sodium, potassium and chloride reabsorption.

In normal circumstances, the reabsorption of sodium at this location creates a hypertonic gradient, which causes water reabsorption via osmosis from the descending loop of Henle. Loop diuretics reduce sodium reabsorption, thereby reducing the hypertonicity in the interstitium of the medulla and leading to reduced reabsorption (and therefore increased excretion) of water.

As up to 20% of the filtered sodium is reabsorbed in the loop of Henle, loop diuretics can exert a much greater effect on sodium reabsorption than any other diuretic acting elsewhere in the nephron, and cause the most profuse diuresis.

Loop diuretics must reach a certain concentration in the tubular lumen to have an effect. Further dose increases will then continue to produce additional diuresis until a maximum ‘ceiling’ concentration has been reached. It is believed that cotransporter mechanisms become saturated at this point, and increasing the dose further will not offer any additional benefits but can increase the risk of side effects.

Furosemide and bumetanide both act within one hour of oral administration and stop having an effect after around six hours, after which rebound reabsorption of sodium further in the tubule may occur. This is known as a “braking” effect, and is a self-protection mechanism by the kidneys, activated to prevent dehydration.

Rebound sodium reabsorption can be prevented by increasing the frequency of diuretic administration or reducing sodium intake.

Hypotenaemia is a common side effect of loop diuretics and is caused by increases in sodium excretion. In normal circumstances, some of the potassium that is reabsorbed by the Na+/K+/2Cl- cotransporter is recycled back into the tubular fluid, which drives further sodium, calcium and magnesium reabsorption. Loop diuretics inhibit potassium recycling, resulting in reduced calcium and magnesium reabsorption.

Loop diuretics also have the potential to cause hypokalaemia and metabolic alkalosis. This is because the inhibition of sodium reabsorption at the loop of Henle results in increased sodium reabsorption further along the kidney tubule (in the late distal tubule and collecting duct), at the expense of hydrogen and potassium reabsorption. Loop diuretics can also cause distal compensation: increased reabsorption of sodium in the distal convoluted tubule.

High doses of loop diuretics may lead to transient or permanent deafness, which may be caused by the diuretic binding to an isozyme of the Na+/K+/2Cl- cotransporter in the inner ear. The risk of the side effect can be minimised by infusing intravenous preparations slowly (e.g. 4mg/min maximum for furosemide), avoiding concomitant use with other medicines that can cause toxicity in the ear and avoiding prolonged use where possible.

Loop diuretics are mainly prescribed for oedema and are not generally used to manage hypertension unless fluid overload is a contributing factor. When using diuretics to reduce fluid load, the patient’s weight and fluid balance should be monitored regularly. Weight loss should be no more than 0.5–1kg per day, which is equivalent to a negative fluid balance of 500–1000ml per day: any greater and the patient is at increased risk of hypovolaemia, hypotension and acute kidney injury.

Bumetanide is the loop diuretic of choice for patients with significant gut oedema. This is because its absorption profile is more predictable than that of furosemide.

**Thiazides and related diuretics**

Thiazides and related diuretics inhibit the Na+/Cl- cotransporter in the distal tubule, preventing sodium reabsorption. Thiazides and related diuretics inhibit approximately 3% to 8% of sodium reabsorption, and so exert a much smaller diuretic effect than loop diuretics. They are therefore considered ‘low ceiling’ diuretics. However, they are potent and small doses can have profound effects.

Thiazides and related diuretics are transported into the tubule in exchange for uric acid. This can lead to raised serum uric acid levels and may precipitate gout. Continuation of thiazide therapy...
Diuretic sites of action
The different classes of diuretic have distinct sites of action which determines their effectiveness and side effect profile

Thiazides and related diuretics can become relatively ineffective in patients with severe chronic kidney disease (stages 4 and 5) if they are not prescribed with a loop diuretic. They can also be highly effective if used in combination with loop diuretics to treat resistant oedema. The medicines most commonly used in combination with loop diuretics are metolazone and bendroflumethiazide. Metolazone is effective for patients with a glomerular filtration rate of <20ml/min. It is believed to have a secondary site of action in the proximal convoluted tubule.

Potassium-sparing diuretics
Potassium-sparing diuretics can be divided into two groups: sodium channel blockers (triamterene and amiloride) and aldosterone antagonists (spironolactone and eplerenone). They act in the late distal tubule and the collecting duct, where just 2–3% of sodium reabsorption occurs. Normally, cells in the collecting duct retain sodium by reabsorbing sodium ions through sodium channels, which is then exchanged with potassium from the interstitial fluid due to the action of the enzyme Na⁺/K⁺ adenosine triphosphatase (Na⁺/K⁺-ATPase). The potassium drawn in to the cell is then excreted into the lumen by potassium channels and lost in urine.

Sodium channel blockers inhibit the sodium channels of principal cells. This...
potassium levels in the body. This reduces sodium reabsorption and leads to the excretion of sodium and water.

Aldosterone is a hormone that causes sodium reabsorption and reduces potassium excretion. It increases the number of active sodium channels and activity of the enzyme Na+/K+ ATPase, which results in increased sodium reabsorption and reduced potassium excretion.

Spironolactone and eplerenone bind to the aldosterone receptor and reduce its activity. This reduces the number of active sodium channels and reduces sodium reabsorption and potassium excretion.

Eplerenone is used to treat severe hyperaldosteronism, the excess secretion of aldosterone that can occur in patients with renal disease or who are taking an ACE inhibitor, angiotensin-II receptor antagonist, or potassium supplements.

Eplerenone has been licensed for the treatment of ascites in cirrhosis.

Potassium-sparing diuretics should be used with caution in patients with renal disease and potassium levels should be monitored regularly for all patients.

References

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Check Your Learning
Loop diuretics reach a maximum ceiling concentration where increases in dose do not have an additional therapeutic effect.

TRUE or FALSE

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