Diuretics

Introduction

Diuretics enhance the rate of excretion of sodium ions (Na+) and water. They are usually taken in the morning so that diuresis does not intrude upon sleep. Diuretics are divided into groups based on their mechanism and site of action: loop, thiazide, potassium-sparing, osmotic, mercurial and carbonic anhydrase inhibitors (*Figure 1*). Only the first three types will be discussed here as they are the ones commonly used.

Loop diuretics

Mode of action

Loop diuretics are potent, act fast and have a short duration of action. They act primarily on the ascending loop of Henle and inhibit electrolyte re-absorption into the interstitial tissue which reduces water re-absorption and hence results in increased diuresis. Furosemide and bumetanide are commonly used.

Adverse effects

Loop diuretics can cause a range of fluid and electrolyte imbalances, including dehydration, hyponatraemia, hypochloraemic metabolic alkalosis, hypokalaemia, hypocalcaemia and hypomagnesaemia.

Cardiac toxicity can be caused by low potassium levels, so caution is advised when prescribing loop diuretics concomitantly with cardiac glycosides.

Hypovolaemia can lead to hypotension which can present as dizziness, light-headedness or confusion, and may result in collapse.

Ototoxicity is associated with elevated concentrations of the drug in the blood, which increases when the drug is prescribed intravenously at high doses, or with concomitant ototoxic drugs, and/or to a patient who has renal impairment. The effect is mostly transient but permanent hearing loss has been reported in some patients who were prescribed furosemide. To reduce the risk of ototoxicity the manufacturers recommend intravenous furosemide should be administered at a maximum rate of 4 mg/minute.

Myalgia is common in patients prescribed intravenous bumetanide, and can occur with oral therapy. This adverse effect was dose related and observed in patients who were exposed to high doses with or without chronic renal impairment. Many avoid intravenous bumetanide and substitute furosemide.

Dosage and monitoring

The risk of adverse effects is higher after large doses and/or prolonged use. Serum electrolytes, blood pressure and weight should be monitored when loop diuretics are newly prescribed.

In chronic heart failure patients, high-dose furosemide and bumetanide given by continuous infusion has been shown to be more effective than the same dose given by bolus injection. Intravenous loop diuretics should be given by either continuous or intermittent infusion which will both enhance diuresis and reduce the risk of toxicity.

Thiazide diuretics

Mode of action

Thiazides are moderately potent diuretics. They act primarily at the beginning of the distal convoluted tubule, inhibiting sodium re-absorption and hence increasing diuresis. The most commonly used thiazide in UK is bendroflumethiazide.

Adverse effects

Postural hypotension occurs as a result of decreased blood volume following diuresis.

Cardiac toxicity can be caused by low potassium levels, so caution is advised when prescribing concomitantly with cardiac glycosides.

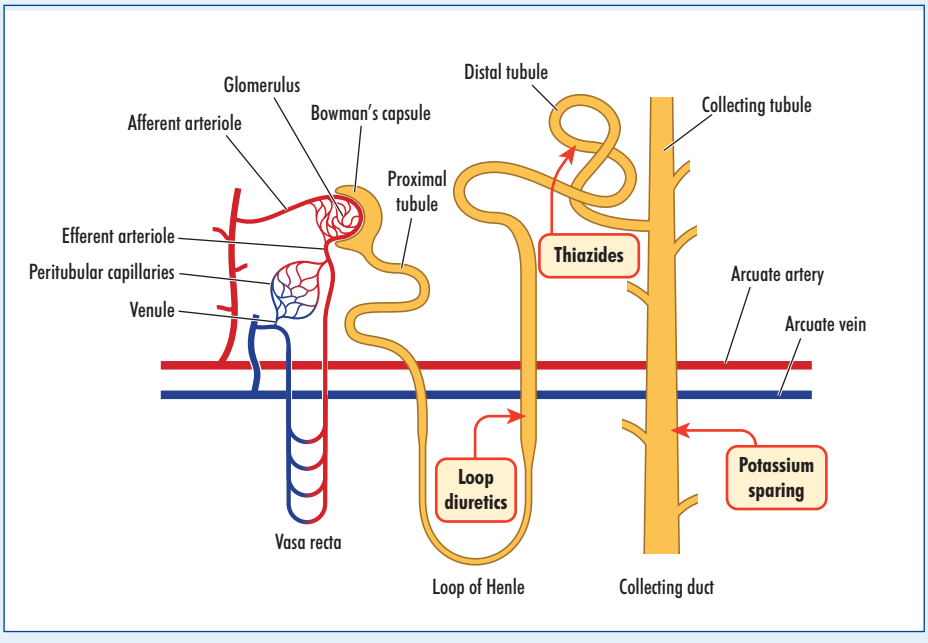
Thiazide diuretics can cause a range of fluid and electrolyte imbalances, including hypokalaemia, hyponatraemia, hypochloraemic metabolic alkalosis, hypercalcaemia and hypomagnesaemia.

Gout is caused by decreased excretion of uric acid and subsequent hyperuricaemia.

Carbohydrate intolerance and consequently hyperglycaemias have been reported in those with a predisposition to diabetes, so their use should be avoided.

Other commonly seen adverse effects are hyperlipidaemia and mild gastrointestinal disturbances.

Figure 1. Overview of the site of action of commonly used diuretics in a nephron.



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Dosage and monitoring

Points to consider when prescribing thiazides are dose–response and adverse effects. Thiazides have a flat dose–response curve when used for the management of hypertension. Bendroflumethiazide 2.5 mg daily produces maximum benefit with little adverse effects. Above this dose there is a marked increase in adverse effects but little or no extra diuresis. Bendroflumethiazide should be avoided if creatinine clearance is less than 30 ml/min as it is ineffective.

Blood pressure, electrolytes, uric acid, glucose and lipids levels should be monitored when thiazides are newly prescribed.

Potassium-sparing diuretics

Mode of action

Potassium-sparing diuretics act primarily on the distal collecting tubules, increasing the excretion of sodium and reducing excretion of potassium. The most commonly used potassium-sparing diuretics are amiloride (a weak diuretic) and spironolactone; the latter is also an aldosterone receptor antagonist and will be discussed separately.

Amiloride

Adverse effects

Amiloride-induced hyperkalaemia is more prevalent in elderly patients, patients with diabetes, patients with renal impairment and those prescribed angiotensin-converting enzyme (ACE) inhibitors or angiotensin antagonists and, in some patients, has resulted in life-threatening cardiac arrhythmias. In some patients, hyponatraemia has been reported when amiloride was prescribed with other diuretics. Patients may also complain of thirst and dizziness.

Amiloride is administered orally, preferably with food to decrease adverse gastrointestinal effects.

Dosage and monitoring

Prescribing points associated with this drug relate to its adverse effects and the renal function of the patient. Caution is needed for patients with diabetes and patients with significant hepatic or renal disease.

Serum electrolytes and renal function should be monitored when amiloride is newly prescribed.

Spironolactone

Additional modes of action

Spironolactone, in addition to being a potassium-sparing diuretic, competitively inhibits aldosterone's action on the distal collecting tubules, myocardium and vasculature.

The renal effects of the drug include increased excretion of sodium chloride and water, and decreased excretion of potassium. Its effects are most pronounced in patients with aldosteronism. It has a slow onset of action, requiring 2 or 3 days for maximum effect, and a prolonged action lasting 2 or 3 days after discontinuation.

Adverse effects

Adverse effects of the drug are mild and respond to withdrawal of the drug.

Hyperkalaemia is seen, particularly in the elderly, in patients with significant renal and hepatic impairment and in those prescribed supplementary potassium, ACE inhibitors or angiotensin antagonists. Fatal cardiac irregularities may occur.

Hyponatraemia is more likely to occur when administered in combination with other diuretics.

Endocrine effects in males include gynaecomastia, decreased libido and impotence; the former appears to be related to both dose and duration of treatment. In females, hirsutism, deepening of the voice, menstrual irregularities, amenorrhoea, postmenopausal bleeding or breast soreness have been reported.

Dosage and monitoring

Caution has to be exercised for the elderly, patients with diabetes, and those with some degree of renal or hepatic impairment. The fluid and electrolyte levels need to be monitored (*Table 1*).

Combination therapy

Combination diuretic therapy can enhance clinical outcome in patients with oedema resistant to one diuretic. Loop diuretics plus a thiazide is the commonly used combination. Loop diuretics act on the ascending loop of Henle and thiazides on the distal convoluted tubules and both inhibit electrolyte re-absorption. Sequential blockade results in decreased reabsorption of electrolytes compared with individual diuretic therapy and, hence, enhanced diuresis as a result of synergistic mechanisms. Furosemide and metolazone is a useful combination because metolazone works at lower levels of

Table 1. Prescribing points for diuretics

Diuretics are usually prescribed in the morning, so that diuresis does not intrude upon sleep. Split doses should not be given after 6 pm
Monitor serum electrolytes and renal function for all diuretics. In addition, blood pressure and weight should be monitored for loop diuretics, and blood pressure, uric acid, glucose and lipids for thiazides
Intravenous furosemide should be administered at a maximum of 4 mg per minute in order to reduce the risk of toxicity
Spironolactone has a slow onset of action, requiring 2 or 3 days for maximum effect and a prolonged action lasting 2 or 3 days after discontinuation
High dose furosemide and bumetanide given intravenously by continuous infusion is more effective than the same dose given by bolus injection
Caution is advised when diuretics is prescribed for the elderly, patients with diabetes, or patients with cardiac, renal or hepatic impairment
Furosemide, bumetanide and bendroflumethiazide decrease serum potassium levels. Caution is advised when prescribed concomitantly with cardiac glycosides as low potassium levels may result in cardiac toxicity
Amiloride and spironolactone increase serum potassium levels; if unchecked this can result in fatalities
Amiloride should be administered orally with food to decrease adverse gastrointestinal effects
Loop diuretics plus thiazide are used in combination in patients with oedema resistant to one diuretic. Prescribing combined diuretic formulations is not preferred as dose optimization of individual constituents is very difficult

glomerular filtration than bendroflumethiazide. Caution is needed when using metolazone because of the severe hyponatraemia that can occur after a few days. Patients discharged on metolazone should be followed up assiduously. Amiloride 5 mg/day may be prescribed with loop diuretics to minimize the risk of hypokalaemia. Fixed dose combined diuretic formulations are not favoured as dose optimization of individual constituents is very difficult. **BJHM**

Conflict of interest: Dr Shakur is a council member for the Royal Society of Medicine's Research and Pharmaceutical section.

KEY POINTS

- Diuretics are very effective means of diuresing patients, but care must be taken to appreciate their differing side-effect profiles.
- Prescribers should actively monitor patients electrolytes during treatment to identify early cases of renal impairment.
- Care must be taken to appreciate the differing mode of actions of differing diuretics when using in combination therapy.
- Always inform patients of possible side effects and their symptoms before initiating therapy.