Diuretics

Diuretics increase urine excretion of both water and electrolytes and are commonly called 'water tablets'. In general, they inhibit electrolyte reabsorption from the lumen of the nephron, increasing osmolarity and enhancing water excretion.

Diuretics have different clinical uses, depending on their sites and mechanisms of action. The sub-classes of diuretics include:

- Thiazides (eg, bendroflumethiazide, hydrochlorothiazide and the thiazide-like diuretic indapamide) are used mainly in low dose in the treatment of hypertension but also, in the case of metolazone, in combination with loop diuretics to treat severe heart failure.
- Loop diuretics (eg, furosemide, bumetanide, torasemide) are widely used for the symptomatic treatment of heart failure and fluid retention in chronic kidney disease. [1]
- Potassium-sparing diuretics (eg, amiloride, triamterene) are weak diuretics, whereas spironolactone and eplerenone are used in the treatment of hypertension, for oedema of liver failure and in heart failure. **NB**: spironolactone and eplerenone are also called aldosterone antagonists.
- Osmotic diuretics (mannitol) are used in a hospital setting for the treatment of cerebral oedema.
- Carbonic anhydrase inhibitors (acetazolamide) are used for the prophylaxis of mountain sickness (unlicensed indication) and glaucoma.

Main indications

Hypertension

See also the separate Hypertension Treatment article.

- Current guidelines from the National Institute for Health and Care Excellence (NICE) and the Joint British Societies recommend an ACE inhibitor/angiotensin receptor blocker or a calcium-channel blocker as first-line choice for treatment of uncomplicated hypertension, depending on age, diabetes status and ethnicity. However if the patient is already taking a diuretic which is controlling their blood pressure then it should be continued.
- If first-line therapy with a calcium-channel blocker is not tolerated then the guideline recommends the use of a thiazide-like diuretic such as indapamide, in preference to a conventional thiazide diuretic such as bendroflumethiazide.
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- For resistant hypertension (step 4 of the NICE treatment algorithm), low-dose spironolactone can be considered if the serum potassium is equal to or less than 4.5 mmol/L). Remember that patients with reduced glomerular filtration rate are at increased risk of developing hyperkalaemia with spironolactone.

Acute left ventricular failure (LVF)

See also the separate Heart Failure Management article.[1]

- Furosemide (40-80 mg) given as a slow intravenous (IV) injection offloads the pulmonary oedema causing the breathlessness associated with acute LVF. Higher doses may be necessary if the patient has been taking large doses over the longer term. The rapid initial action is due to pulmonary vasodilation rather than the later diuretic effect.
- Eplerenone is licensed for use as an adjunct in LVF following myocardial infarction.[2] [3]

Chronic heart failure[4]

- Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure and titrated (up and down) according to need following the initiation of subsequent heart failure therapies.
- People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics.

- Spironolactone is not mentioned in the NICE guidance on heart failure but does appear in the European Society of Cardiology guideline where it is recommended in all patients with heart failure with reduced ejection fraction, after the use of an ACE inhibitor and a beta-blocker.[5]
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Liver failure and ascites[6]

See also the separate Ascites article.

- Spironolactone is particularly useful for the secondary hyperaldosteronism associated with hepatic cirrhosis and is the diuretic of choice to control resultant ascites and oedema. Treatment must be stopped if encephalopathy develops.
- For recurrent ascites and where a faster diuresis is needed, spironolactone may be combined with furosemide.
- Spironolactone can also be used to treat malignant ascites.

Combination therapy

- **Thiazide and loop diuretic** - indicated in refractory heart failure where there is an inadequate response to a loop diuretic alone. This combination can cause dramatic diuresis with resultant dehydration, hypovolaemia, hyponatremia and hypokalaemia. This would generally be initiated in secondary care, either during an admission or in the outpatient clinic. Dose titration should be gradual with adequate clinical and biochemical monitoring. Heart failure specialist nurses may be helpful in this situation.
- **Potassium-sparing diuretic and thiazides** - the addition of a potassium-sparing diuretic may be useful in those who develop hypokalaemia on thiazide therapy.
- **Potassium-sparing diuretic and loop diuretic** - a potassium-sparing diuretic can again be added to those who develop, or are at high risk of, developing hypokalaemia.
- **Spironolactone and loop diuretic** - spironolactone can be used as a potassium-sparing diuretic for patients on loop diuretics who are at risk of hypokalaemia.

Combination products - for example, co-amilofruse (furosemide and amiloride) - may be indicated where a patient is stable on a fixed dose of loop/thiazide and potassium-sparing diuretics where a single preparation may aid compliance. However, combination products are less flexible - changing the dose of one component will alter the dose of the other component without necessarily producing the optimal therapeutic response. Also, routine prescribing of combination products is poor practice: amiloride is frequently not required since many heart failure patients will also be on an ACE inhibitor which has a potassium-sparing effect.

Common problems

Potassium loss

- Hypokalaemia can occur with loop or thiazide diuretics. The risk of hypokalaemia is related to duration of action as well as potency, so is actually greater with an equipotent dose of thiazide compared to loop diuretic.
- Avoid loop diuretics and thiazides (or consider prophylactic use of a potassium-sparing diuretic) in:
    - Patients with pre-existing hypokalaemia.
    - Patients where hypokalaemia could have serious consequences (eg, those on digoxin and other anti-arrhythmic drugs, patients with severe coronary heart disease).
    - Situations where concomitant medication is likely to lower potassium further (eg, steroids, potent laxatives).
- Potassium-sparing diuretics are not particularly potent and should generally be avoided in heart failure patients where loop diuretics are more efficacious and patients are likely also to be taking ACE inhibitors.
- Spironolactone can be used as a potassium-sparing diuretic in cardiac failure.

- Only prescribe potassium-sparing diuretics where a patient has, or is at risk of, hypokalaemia. They offer a more effective alternative to potassium supplements. However, they are not a guarantee against hypokalaemia, so monitoring is still mandatory.
- Hypokalaemia in liver failure can precipitate encephalopathy, particularly in alcoholic cirrhosis.

Additional electrolyte disturbances such as hyponatremia and hypomagnesaemia may occur, particularly at higher doses of diuretic therapy, due to increased renal excretion. Hyperuricaemia and metabolic alkalosis are also risks.

Metabolic disturbance

Hyperglycaemia and increased insulin resistance are associated with thiazide diuretic use. .

Hypotension

Acute hypotension may be induced where aggressive diuresis has been undertaken, particularly with a loop diuretic or combination therapy:

- Ensure a patient is not hypovolaemic before starting diuretics, since diuresis occurs from the intravascular space.
- The diuresis associated with diuretics is dose-related. Excessive doses of diuretics can cause hypotension and dehydration without relieving oedema (which is still in the extravascular space).
- The usual maximum target rate of fluid loss is one litre per day.
- Previous treatment with diuretics increases the risk of first-dose hypotension when starting ACE inhibitors. Stop the diuretic for two days (where possible) before starting an ACE inhibitor and give the first dose with the patient lying down.

Postural hypotension is common with thiazides and loop diuretics and most likely in elderly patients. If possible, withdraw offending drugs or reduce the dose. Advise the patient to stand up slowly and in stages. Compression stockings may assist if venous insufficiency contributes.

Kidney injury/renal impairment

- At high doses, diuretics may cause a pre-renal uraemia.

- Renal toxicity with diuretics occurs frequently, especially amongst the elderly, via diminished renal excretion, altered plasma protein binding and interactions with other drugs such as non-steroidal anti-inflammatory drugs (NSAIDs). Remember that renal function may diminish over time or with concurrent illness.
- High doses of furosemide may be required in moderate-to-severe renal impairment.
- Patients with renal insufficiency are at risk of hyperkalaemia, so potassium-sparing diuretics are **not** usually indicated.
- Patients with heart failure and concomitant severely impaired renal function often require very large doses of diuretics - specialised help is recommended.

Requests for unnecessary use of diuretics

Diuretics are sometimes abused by sportsmen and sportswomen who need to lose weight rapidly to make a weight class - eg, in boxing or horse racing. Patients may also request diuretics to treat idiopathic oedema or that due to gravity, obesity, venous stasis or lymphoedema - this should be avoided, as any initial benefit is usually offset by tolerance and worsening oedema.

Contra-indications and cautions

See individual drug monographs for a full list.

In general:

- **Renal impairment** - there is an increased risk of hyperkalaemia with potassium-sparing diuretics and spironolactone. Thiazides are ineffective with increasing severity of impairment.
- **Severe liver disease** - thiazides and loop diuretics should be used with extreme caution, as hypokalaemia may precipitate hepatic coma. High doses of spironolactone are sometimes necessary in the treatment of cirrhosis - seek specialised help.
- **Elderly** - use lower initial doses since the elderly are particularly susceptible to diuretic side-effects. Adjust the dose according to renal function. Avoid long-term use of diuretics to shift gravitational oedema - increasing muscle pump activity, raising the legs at rest and use of support stockings are more appropriate.

- **Pregnancy** - there is a risk of volume depletion and fetal/neonatal toxicity associated with diuretics. One study suggested that women using loop diuretics during pregnancy gave birth to heavier infants and had a higher risk of preterm birth; however, there were confounding factors.[7] Methyldopa, nifedipine and labetalol are used to treat hypertension in pregnancy and thiazides should be avoided.
- **Gout** - thiazides and loop diuretics can precipitate or worsen pre-existing gout. If a diuretic is unavoidable, consider prophylaxis with allopurinol.

Initiating diuretics

- Check electrolytes and renal function prior to starting treatment and correct any pre-existing hypokalaemia.
- Check blood pressure and fluid status - avoid diuresis where there is evidence of hypovolaemia.
- Check blood glucose and lipids - pre-existing glucose intolerance or hyperlipidaemia may be worsened by thiazides or loop diuretics.

Monitoring diuretics

- Thiazides in the low dose used to treat hypertension are unlikely to cause major electrolyte disturbance:
    - Re-check blood pressure, renal function and electrolytes within 4-6 weeks of commencing therapy.
    - If blood pressure is not adequately controlled by a low dose of thiazide, an additional antihypertensive agent should be considered rather than increasing the dose.
    - Where blood pressure, renal function and electrolytes are satisfactory, review every 6-12 months unless the patient's clinical condition changes or interacting drugs are added.

- With loop diuretics:
    - Re-check renal function and electrolytes 1-2 weeks after commencing therapy and after increasing the dose. This should be done earlier (within 5-7 days) if there is pre-existing renal impairment or where the patient is already receiving an ACE inhibitor (or AGT2 receptor antagonist) or aldosterone antagonist.
    - Once stable, six-monthly renal function tests should suffice unless there is any change in therapy, intercurrent illness or worsening renal impairment. However, more frequent monitoring is still advised in those at higher risk.[4]
- With combined loop and thiazide diuretics:
    - Check renal function and electrolytes within five days of starting and then every 5-14 days, depending on an individual's stability.
    - Monitor weight and hydration status and, where diuresis is extensive, consider earlier testing of renal function.
    - Once stable, six-monthly checks may suffice unless there is any change in therapy, intercurrent illness or worsening renal impairment.

- With spironolactone:
    - Check renal function and electrolytes at 1, 4, 8 and 12 weeks. Thereafter at 6, 9 and 12 months and then on a six-monthly basis.
    - If hyperkalaemia occurs (between 5.5 mmol/L and 5.9 mmol/L) or serum creatinine rises to ≥220 micromol/L on spironolactone, halve the dose to 25 mg on alternate days and recheck U&Es frequently.
    - A potassium level ≥6.0 mmol/L or a creatinine level >310 micromol/L, should prompt the immediate stopping of spironolactone and the seeking of specialist advice.
    - Eplerenone should be monitored in the same way as spironolactone.
- Daily weights can help monitor fluid loss with cardiac oedema or ascites. With ascites, aim for a weight reduction of no more than 0.5 kg/day.
- Compliance - many patients find that diuresis interferes with their daily activity. Discuss with the patient to find the most convenient time to take their diuretic - it may not necessarily be first thing in the morning.

Onset and duration of action of diuretics [8]

- **Thiazides** - onset of diuresis within 1-2 hours of oral administration. Duration varies with drug - bendroflumethiazide 6-12 hours, chlortalidone 24-72 hours. They are usually prescribed *mane* in order to avoid night-time disruption.
- **Loop diuretics** - rapid onset of diuresis, less than one hour after oral administration. Duration approximately six hours, so twice-daily dosing is possible.

Referral criteria

- Inadequate response to therapy.
- Poor tolerance of drugs.

- Deteriorating renal function.

Patient advice

- Explain indication for use of diuretic (or 'water tablet').
- Explain frequency of initial monitoring and how blood tests/reviews will be arranged and followed up.
- Diuretics usually make people need to pass urine more frequently. Enquire about difficulties getting to the toilet in time and disruption to sleep or daytime activities.
- Patients can be educated to increase diuretic doses - for example, if they have worsening symptoms of heart failure - or can be educated to adjust dose timing to suit their daily needs.
- Side-effects such as impotence should be mentioned, since patients may not volunteer these themselves.
- Advise that some over-the-counter medications, such as NSAIDs, may interact with their diuretic and that patients should check with pharmacists/their doctor before taking additional medicines.
- Advise avoiding the use of salt substitutes that are high in potassium, with aldosterone antagonists or potassium-sparing diuretics.

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