

Diuretics

Diuretics increase urinary excretion of water and electrolytes and are used to relieve oedema associated with heart failure, nephrotic syndrome or hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are mainly used to treat cerebral oedema, and also to lower raised intraocular pressure.

Most diuretics increase urine volume by inhibiting the reabsorption of sodium and chloride ions in the renal tubule; they also modify renal handling of potassium, calcium, magnesium and urate. Osmotic diuretics act differently; they cause an increase in urine volume by an osmotic effect.

Although **loop diuretics** are the most potent their duration of action is relatively short, whilst **thiazide diuretics** are moderately potent but produce diuresis for a longer period. **Potassium-sparing diuretics** are relatively weak. Carbonic anhydrase inhibitors are weak diuretics which are rarely used for their diuretic effect and are principally used to lower intraocular pressure in glaucoma (section 21.4.4).

ELECTROLYTE IMBALANCE

The adverse effects of diuretic therapy are mainly due to the fluid and electrolyte imbalance induced by the drugs. *Hyponatraemia* is an adverse effect of all diuretics. The risk of *hypokalaemia*, which may occur with both thiazide and loop diuretics, depends more on the duration of action than on potency and is thus greater with thiazides than with loop diuretics (when given in equipotent doses). Potassium-sparing diuretics can cause *hyperkalaemia*. Other electrolyte disturbances include *hypercalcaemia* (thiazides), *hypocalcaemia* (loop diuretics) and *hypomagnesaemia* (thiazide and loop diuretics).

Symptoms of fluid and electrolyte imbalance include dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias.

ELDERLY

The elderly are more susceptible to electrolyte imbalance than younger patients. Treatment should begin with a lower initial dose of the diuretic (commonly about 50% of the adult dose) and then adjusted carefully according to renal function, plasma electrolytes and diuretic response.

Thiazide diuretics

Thiazide diuretics, such as **hydrochlorothiazide**, are moderately potent and act by inhibiting sodium and chloride reabsorption at the beginning of the distal convoluted tubule. They produce diuresis within 1–2 hours of oral administration and most have a duration of action of 12–24 hours.

Thiazide diuretics are used in the management of oedema associated with mild to moderate congestive heart failure, renal dysfunction or hepatic disease; however, thiazides are not effective in patients with poor renal function (creatinine clearance of less than 30 ml per minute). In severe fluid retention a loop diuretic may be necessary.

In hypertension, a thiazide diuretic is used at a low dose to lower blood pressure with very little biochemical disturbance; the maximum therapeutic effect may not be seen for several weeks. Higher doses should not be used because they do not necessarily increase the hypotensive response but may cause marked changes in plasma potassium, magnesium, uric acid, glucose and lipids. If a thiazide alone does not lower blood pressure adequately, it may be used in combination with another antihypertensive such as a beta-adrenoceptor antagonist (section 12.3).

Urinary excretion of calcium is reduced by thiazide diuretics and this property is occasionally utilized in the treatment of idiopathic hypercalciuria in patients with calcium-containing calculi. Paradoxically, thiazide diuretics are used in the treatment of diabetes insipidus, since in this disease they reduce urine volume.

Thiazide diuretics, especially in high doses, produce a marked increase in potassium excretion which may cause hypokalaemia; this is dangerous in patients with severe coronary artery disease and those being treated with cardiac glycosides. In hepatic failure hypokalaemia can precipitate encephalopathy, particularly in alcoholic cirrhosis. Potassium-sparing diuretics are used as a more effective alternative to potassium supplements for prevention of hypokalaemia induced by thiazide diuretics; however supplementation with potassium in any form is seldom necessary with the smaller doses of diuretics used to treat hypertension.

Hydrochlorothiazide

Hydrochlorothiazide is a representative thiazide diuretic. Various drugs can serve as alternatives

Tablets , hydrochlorothiazide, 25 mg, 50 mg

Uses:

oedema; diabetes insipidus; hypertension (see also section 12.3); heart failure (section 12.4)

Contraindications:

severe renal or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease

Precautions:

renal (Appendix 4), hepatic impairment (Appendix 5); pregnancy (Appendix 2), breastfeeding (Appendix 3); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria; **interactions:** Appendix 1

Dosage:

Hypertension, *by mouth*, **ADULT** 12.5–25 mg daily; **ELDERLY** initially 12.5 mg daily

Oedema, *by mouth*, **ADULT** initially 25 mg daily on rising, increasing to 50 mg daily if necessary; **ELDERLY** initially 12.5 mg daily

Severe oedema in patients unable to tolerate loop diuretics, *by mouth*, **ADULT** up to 100 mg *either* daily *or* on alternate days (maximum 100 mg daily)

Nephrogenic diabetes insipidus, *by mouth*, **ADULT** initially up to 100 mg daily

Adverse effects:

hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis (for symptoms of fluid and electrolyte imbalance see introductory notes); hypercalcaemia; hyperglycaemia; hyperuricaemia, gout; rash, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible), blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis and hypersensitivity reactions (including pneumonitis, pulmonary oedema, severe skin reactions) also reported; acute renal failure

Loop diuretics

Loop diuretics, or high-ceiling diuretics, such as **furosemide**, are the most potent and rapidly produce an intense dose-dependent diuresis of relatively short duration. Oral furosemide produces diuresis within 30–60 minutes of administration, with the maximum diuretic effect in 1–2 hours. The diuretic action lasts for 4–6 hours. Intravenous furosemide produces diuresis within 5 minutes, with the maximum diuretic effect in 20–60 minutes and diuresis complete within 2 hours.

Loop diuretics inhibit reabsorption from the ascending loop of Henlé in the renal tubule and are useful, particularly in situations where rapid and effective diuresis is needed such as reduction of acute pulmonary oedema due to left ventricular failure. They are also used to treat oedema associated with renal and hepatic disorders and are used in high doses in the management of oliguria due to chronic renal insufficiency. Loop diuretics may be effective in patients unresponsive to thiazide diuretics.

Because of their shorter duration of action, the risk of hypokalaemia may be less with loop diuretics than with thiazide diuretics; if required, potassium-sparing diuretics may be used for prevention of hypokalaemia. Loop diuretics may cause hypovolaemia and excessive use can produce severe dehydration with the possibility of circulatory collapse. Furosemide may cause hyperuricaemia and precipitate attacks of gout. Rapid high-dose injection or infusion of furosemide may cause tinnitus and even permanent deafness.

Furosemide

Furosemide is a representative loop diuretic. Various drugs can serve as alternatives

Tablets, furosemide 40 mg

Injection (Solution for injection), furosemide 10 mg/ml, 2-ml ampoule

Uses:

oedema; oliguria due to renal failure

Contraindications:

renal failure with anuria; precomatose states associated with liver cirrhosis

Precautions:

monitor electrolytes particularly potassium and sodium; hypotension; elderly (reduce dose); pregnancy (Appendix 2), breastfeeding (Appendix 3); correct hypovolaemia before using in oliguria; renal impairment (Appendix 4), hepatic impairment (Appendix 5); prostatic enlargement; porphyria; **interactions:** Appendix 1

Dosage:

Oedema, *by mouth*, **ADULT** initially 40 mg daily on rising; maintenance, 20–40 mg daily; may be increased to 80 mg daily or more in resistant oedema; **CHILD** 1–3 mg/kg daily (maximum 40 mg daily)

Acute pulmonary oedema, *by slow intravenous injection*, **ADULT** 20–50 mg, if necessary increase by 20-mg steps every 2 hours; if effective single dose is more than 50 mg, consider using *slow intravenous infusion* at a rate not exceeding 4 mg/minute; **CHILD** 0.5–1.5 mg/kg daily (maximum 20 mg daily)

Oliguria (glomerular filtration rate less than 20 ml/minute), *by slow intravenous infusion* at a rate not exceeding 4 mg/minute, **ADULT** initially 250 mg over 1 hour; if urine output not satisfactory during hour after first dose, infuse 500 mg over 2 hours then, if no satisfactory response during hour after second dose, infuse 1 g over 4 hours; if no response after third dose, dialysis probably necessary

NOTE. Dose to be diluted in suitable amount of infusion fluid, depending on hydration of patient

Adverse effects:

hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis (for symptoms of fluid and electrolyte imbalance, see introductory notes), increased calcium excretion, hypovolaemia, hyperglycaemia (but less often than with thiazide diuretics); temporary increase in plasma cholesterol and triglyceride concentration; less commonly hyperuricaemia and gout; rarely rash, photosensitivity, bone marrow depression (withdraw treatment), pancreatitis (with large parenteral doses), tinnitus and deafness (with rapid administration of large parenteral doses and in renal impairment; deafness may be permanent if other ototoxic drugs taken)

Potassium-sparing diuretics

Potassium-sparing diuretics include **amiloride** and **spironolactone** ; they are weak diuretics and reduce potassium excretion and increase sodium excretion in the distal tubule. Amiloride acts about 2 hours after oral administration, reaching a peak in 6–10 hours and persisting for about 24 hours. Spironolactone, which acts by antagonising aldosterone, has a relatively slow onset of action requiring 2–3 days to achieve maximum diuretic effect, and a similar period of 2–3 days for diuresis to cease after discontinuation of treatment.

Amiloride may be used alone, but its principal use is in combination with a thiazide or a loop diuretic to conserve potassium during treatment of congestive heart failure or hepatic cirrhosis with ascites.

Spironolactone is used in the treatment of refractory oedema due to heart failure, hepatic cirrhosis (with or without ascites), nephrotic syndrome and ascites associated with malignancy. It is frequently given with a thiazide or a loop diuretic, helping to conserve potassium in those at risk from hypokalaemia. A low dose of spironolactone is beneficial in severe heart failure in patients who are already taking an ACE inhibitor and a diuretic. Spironolactone is used in the diagnosis and treatment of primary hyperaldosteronism; presumptive evidence for diagnosis is provided by correction of hypokalaemia and of hypertension.

The most dangerous adverse effect of potassium-sparing diuretics, such as amiloride or spironolactone, is hyperkalaemia, which can be life-threatening. These diuretics are thus best avoided or used very carefully in patients who have or may develop hyperkalaemia, such as those with renal failure, patients receiving other potassium-sparing diuretics and patients taking ACE inhibitors or potassium supplements.

Amiloride hydrochloride

Tablets , amiloride hydrochloride 5 mg

Uses:

oedema associated with heart failure or hepatic cirrhosis (with ascites), usually with thiazide or loop diuretic

Contraindications:

hyperkalaemia; renal failure

Precautions:

monitor electrolytes, particularly potassium; renal impairment (Appendix 4); diabetes mellitus; elderly (reduce dose); pregnancy and breastfeeding (Appendices 2 and 3);

interactions: Appendix 1

Dosage:

Oedema, used alone, *by mouth*, initially 10 mg daily in 1 or 2 divided doses, adjusted according to response (maximum 20 mg daily)

Combined with a thiazide or a loop diuretic, *by mouth*, initially 5 mg daily, increasing to 10 mg if necessary (maximum 20 mg daily)

Adverse effects:

hyperkalaemia, hyponatraemia (for symptoms of fluid and electrolyte imbalance see introductory notes), diarrhoea, constipation, anorexia; paraesthesia, dizziness, minor psychiatric or visual disturbances; rash, pruritus; rise in blood urea nitrogen

Spirolactone

Tablets, spironolactone, 25 mg

Uses:

refractory oedema in congestive heart failure; adjunct to ACE inhibitor and diuretic in severe congestive heart failure; nephrotic syndrome; hepatic cirrhosis with ascites and oedema; ascites associated with malignancy; primary hyperaldosteronism

Contraindications:

pregnancy (Appendix 2); breastfeeding; hyperkalaemia; hyponatraemia; severe renal impairment; Addison disease

Precautions:

monitor blood urea nitrogen and plasma electrolytes (discontinue if hyperkalaemia); elderly (reduce dose); diabetes mellitus; renal impairment (Appendix 4); hepatic impairment; porphyria; high doses carcinogenic in *rodents*; **interactions:** Appendix 1

Dosage:

Oedema, *by mouth*, **ADULT** 100–200 mg daily, increased if necessary to 400 mg daily in resistant oedema; usual maintenance dose 75–200 mg daily; **CHILD** initially 3 mg/kg daily in divided doses

Primary hyperaldosteronism, *by mouth*, **ADULT**, diagnosis, 400 mg daily for 3–4 weeks (see notes above); preoperative management, 100–400 mg daily; if not suitable for surgery, lowest effective dose for long-term maintenance

Adjunct in severe heart failure, *by mouth*, **ADULT** usually 25 mg daily

Adverse effects:

hyperkalaemia, hyponatraemia, hyperchloraemic acidosis, dehydration (for symptoms of fluid and electrolyte imbalance see introductory notes); transient increase in blood

urea nitrogen; diarrhoea; gynaecomastia, menstrual irregularities; impotence, hirsutism, deepening of voice; rash, ataxia, fever, hepatotoxicity

Osmotic diuretics

Osmotic diuretics, such as **mannitol**, are administered in sufficiently large doses to raise the osmolarity of plasma and renal tubular fluid. Osmotic diuretics are used to reduce or prevent cerebral oedema, to reduce raised intraocular pressure or to treat disequilibrium syndrome. Mannitol is also used to control intraocular pressure during acute attacks of glaucoma. Reduction of cerebrospinal and intraocular fluid pressure occurs within 15 minutes of the start of infusion and lasts for 3–8 hours after the infusion has been discontinued; diuresis occurs after 1–3 hours.

Circulatory overload due to expansion of extracellular fluid is a serious adverse effect of mannitol; as a consequence, pulmonary oedema can be precipitated in patients with diminished cardiac reserve, and acute water intoxication may occur in patients with inadequate urine flow.

Mannitol

Infusion (Solution for infusion), mannitol 10%, 20%

Uses:

cerebral oedema; raised intraocular pressure (emergency treatment or before surgery)

Contraindications:

pulmonary oedema; intracranial bleeding (except during craniotomy); severe congestive heart failure; metabolic oedema with abnormal capillary fragility; severe dehydration; renal failure (unless test dose produces diuresis)

Precautions:

monitor fluid and electrolyte balance; monitor renal function

Dosage:

. Test dose if patient oliguric or renal function is inadequate, *by intravenous infusion*, as a 20% solution, 200 mg/kg body weight infused over 3–5 minutes; repeat test dose if urine output less than 30–50 ml/hour; if response inadequate after second test dose, re-evaluate patient

Raised intracranial or intraocular pressure, *by intravenous infusion*, as a 20% solution infused over 30–60 minutes, 0.25–2 g/kg body weight

Cerebral oedema, *by intravenous infusion*, as a 20% solution infused rapidly, 1 g/kg body weight

PHARMACEUTICAL PRECAUTIONS. Solutions containing more than mannitol 15% may crystallize during storage, crystals must be redissolved by warming solution before use and solution

must not be used if any crystals remain; intravenous administration sets must have a filter; mannitol should not be administered with whole blood or passed through the same transfusion set as blood

Adverse effects:

fluid and electrolyte imbalance (for symptoms see introductory notes); circulatory overload, acidosis; pulmonary oedema particularly in diminished cardiac reserve; chills, fever, chest pain, dizziness, visual disturbances; hypertension; urticaria, hypersensitivity reactions; extravasation may cause oedema, skin necrosis, thrombophlebitis; rarely, acute renal failure (large doses)