

## DRUG CLASSES

### OTHER DIURETICS

Loop diuretics and potassium sparing diuretics have limited roles in the management of hypertension although accumulating evidence suggests that potassium-sparing diuretics may have an important place in apparently resistant hypertension.

#### LOOP DIURETICS

**Examples** Bumetamide  
Furosemide  
Torasemide

#### Mechanism of action

Loop diuretics act on the nephron mainly in the thick ascending limb of the Loop of Henle. Although loop diuretics have diuretic efficacy greater than that of thiazide or thiazide-like agents, effects on blood pressure are relatively brief and reflex stimulation of the renin-angiotensin system tends to counter the fall in blood pressure.

#### Pharmacokinetics

Loop diuretics are well absorbed after oral administration. Elimination is largely by the renal route with a small contribution from liver metabolism. Like thiazide and thiazide-like diuretics, the renal effects depend on access to the luminal side of the renal tubule; unlike thiazide and thiazide-like diuretics, loop diuretics retain some efficacy in renal impairment.

#### Adverse effects

As with thiazide and thiazide-like diuretics, these are mainly metabolic

- Hypokalaemia is even less common than with low-dose thiazides or thiazide-like diuretics
- Hyperglycaemia is less marked than with thiazide or thiazide-like diuretics

- Urate retention **risk of acute gout**
- Hypocalcaemia due to increased renal clearance of calcium **small risk of ureteric calculi**

### Practical issues

Bumetamide and furosemide have a rapid onset and short duration of action. Twice daily dosing is more effective in lowering blood pressure. However, persistent diuresis may limit utility. Torasemide has a longer duration of action and can be given once daily but metabolic complications, particularly hypokalaemia, are more marked than with other loop- diuretics.

Loop diuretics are recommended in the management of hypertension in three circumstances.

- Where hypertension is complicated by chronic renal impairment (serum creatinine > 150  $\mu\text{mol/l}$ ; eGFR < 45), thiazide or thiazide-like diuretics are usually ineffective since these drugs are not filtered in sufficient concentrations to sites of action in the nephron. Loop diuretics can be substituted but high doses are often needed e.g. furosemide 80 mg twice daily.
- Where co-morbidities provide a compelling indication for a loop diuretic as part of the antihypertensive regimen e.g. heart failure.
- As a **step 4** therapy option as recommended by the NICE/BHS ACD algorithm i.e. individuals with blood pressure above target despite treatment with an ACE inhibitor or angiotensin receptor blocker (A), calcium channel blocker (C) and a thiazide or thiazide-like diuretic (D) each at full dose in combination. Loop diuretics may be used in addition to, or instead of potassium sparing diuretics where there is concern about hyperkalaemia.

Although a history of gout is a compelling contraindication, addition of a loop diuretic may sometimes be necessary to control blood pressure in people with gout, ideally in combination with allopurinol.

### POTASSIUM SPARING DIURETICS

**Examples**      Amiloride  
                          Eplerenone  
                          Spironolactone  
                          Triamterene

### Mechanism of action

Potassium sparing diuretics act on the distal portion of the distal convoluted tubule and in the collecting duct, inhibiting sodium/potassium exchange. Eplerenone and spironolactone are competitive antagonists of the effect of aldosterone at distal tubular sites. All are weak diuretics but are effective antihypertensive agents particularly in low-renin (salt-dependent) hypertension.

### **Pharmacokinetics**

Amiloride is excreted unchanged in the urine while other potassium sparing diuretics undergo hepatic metabolism leading to some active metabolites. Elimination half-life of parent drug and metabolites is variable but has little relation to duration of antihypertensive activity.

### **Adverse effects**

- Hyperkalaemia due to reduced urine potassium loss.
- Hyponatraemia when combined with thiazide or thiazide-like diuretics, particularly in the elderly.
- Endocrine side effects with aldosterone antagonists due to non-specific actions e.g. gynaecomastia in men and menstrual irregularities in women. Eplerenone is more selective than spironolactone making these side effects less common.

### **Practical issues**

All potassium sparing agents appear to reduce blood pressure over 24 hours when given once daily. These drugs are seldom given alone and are not recommended for first-line diuretic therapy. However, monotherapy may be adequate in patients with primary hyperaldosteronism.

Potassium sparing diuretics have two major roles in the management of hypertension.

- Prevention and treatment of hypokalaemia
- Management of resistant hypertension

Prevention of hypokalaemia is important in patients with cardiac arrhythmias, in patients requiring a thiazide or thiazide-like diuretic who have low potassium intake, (e.g. the elderly) and probably in patients at risk of developing glucose intolerance on thiazide or thiazide-like diuretics. Persistent serum potassium below 3.5 mmol/l is associated with a poorer outcome and increased risk of new onset diabetes. This is an indication for potassium correction usually by co-administration of a potassium sparing diuretic. Prescription of a potassium sparing agent is more effective than the use of potassium supplements and has the additional benefit of improving blood pressure control.

There is increasing evidence for the value of potassium sparing diuretics in patients with resistant hypertension i.e. blood pressure above target despite three drugs at full doses in combination and including a thiazide. The added blood pressure reduction may be the result of increased diuresis or inhibition of unsuspected hyperaldosteronism in resistant hypertension. At present, the evidence supports the use of amiloride, sometimes at high doses (20 mg daily) and spironolactone at low doses (12.5 – 50 mg daily). BHS recommendations include low dose spironolactone as a **step 4** treatment option i.e. in patients with blood pressure above target despite a combination of A + C + D. Eplerenone might be considered as an alternative to spironolactone to avoid non-specific side effects such as gynaecomastia. However, the equivalent antihypertensive doses of eplerenone are higher (25 – 100 mg daily) at which doses endocrine side effects may be seen.

Hyperkalaemia, an adverse reaction common to all potassium sparing diuretics, is particularly likely in patients with impaired renal function and in the elderly. This side-effect is silent but may be fatal. Potassium supplements should rarely be required with potassium sparing diuretics but, if combined, close monitoring of serum potassium is necessary. Similar cautions are required with concomitant use of an ACE inhibitor or angiotensin receptor blocker, as these agents also raise serum potassium, and with concomitant use of a non-steroidal anti-inflammatory drug which may impair diuresis, and provoke hyperkalaemia and renal failure. These considerations should not dissuade the prescriber from careful use of potassium sparing diuretics when indicated.

Potassium sparing diuretics are available as proprietary formulations combined with a thiazide (or loop) diuretics. Combination tablets are more expensive but may improve compliance by reducing the number of tablets to be taken.

Outcome data with potassium sparing diuretics is lacking. However, triamterene was used as part of the treatment regimen in the European Working Party on High Blood Pressure in the Elderly (EUWPHE) Study, the first trial to establish the benefit of lowering blood pressure in older people, amiloride was part of the diuretic regimen in INSIGHT, which demonstrated diuretic to be as effective as high-dose nifedipine, and spironolactone was highly effective as a fourth-line option in ASCOT.