

THIAZIDE AND THIAZIDE-LIKE DIURETICS

These drugs have formed the cornerstone of the management of hypertension for several decades. Control of blood pressure may be difficult without the use of a diuretic.

Examples

- Bendroflumethiazide
- Chlortalidone
- Cyclopentiazide
- Hydrochlorothiazide
- Indapamide

Mechanism of action

Thiazide and thiazide-like diuretics act on the nephron mainly at the proximal part of the distal tubule. Sodium excretion and urine volume are increased by interference with transfer across cell membranes. The result is a reduction in blood volume. However, changes in cardiac output and extracellular fluid volume are transient and, in the long-term, the major haemodynamic effect is a reduction in peripheral resistance due to subtle alterations in the contractile responses of vascular smooth muscle.

Pharmacokinetics

Thiazides and thiazide-like diuretics are well absorbed orally, widely distributed and subject to a variable degree of hepatic metabolism. The effect on the kidney depends upon excretion into the renal tubule; efficacy falls with increasing renal impairment.

Adverse effects

These are mainly metabolic

- Hypokalaemia due to urinary potassium loss. Fall in serum potassium > 0.3 mmol/l with low-dose thiazide or thiazide-like diuretics raises suspicion of primary hyperaldosteronism if serum sodium is in high-normal range: **refer for investigation.**
- Hyperuricaemia due to interference with renal clearance of uric acid. **Risk of acute gout**
- Hyperglycaemia possibly related to hypokalaemia. **Risk of new onset diabetes**
- Hypercalcaemia due to reduced renal clearance of calcium
- Erectile dysfunction by an unknown mechanism.
- Thrombocytopaenia and skin rashes. **Rare**

Practical issues

The onset of diuretic effect is usually observed within one hour and may last for about 12 hours. With repeated doses, diuresis diminishes. The antihypertensive effect is more gradual in onset and more long-lasting. On chronic dosing, the antihypertensive effect persists for 24 hours and once-daily dosing is appropriate for most agents.

Antihypertensive effects are seen at low doses and there appears to be little additional blood pressure lowering from higher doses when used as monotherapy. At higher doses, metabolic side effects are much more marked. Current recommendations are to use a low-dose thiazide or thiazide-like diuretic regimen. Efforts should be made to avoid hypokalaemia; co-administration of a potassium-sparing diuretic is preferable to use of potassium chloride supplements.

From cost considerations, bendroflumethiazide 2.5 mg is the thiazide of choice in the UK. Where hypertension is complicated by chronic renal impairment (serum creatinine > 150 µmol/l; eGFR < 45), thiazide diuretics are usually ineffective; a loop diuretic, often at high doses, can be substituted.

Thiazide and thiazide-like diuretics are often used in combination with other antihypertensive agents. No combinations are incompatible but combined use with an ACE inhibitor or angiotensin receptor blocker might be particularly beneficial; antihypertensive effects are at least additive and some metabolic complications (e.g. hypokalaemia) may be reduced. Thiazide and thiazide-like diuretics (usually hydrochlorothiazide at low doses) are available in single pill combinations with other antihypertensives. These preparations may improve compliance and should be considered, provided there is no cost disadvantage.

The evidence base for these drugs in the management of hypertension is strong. Thiazide or thiazide-like diuretics were used in most of the early studies which established the benefit of treating hypertension albeit often at doses far in excess of those currently recommended. More recently, low-dose thiazides have often been included as add-on therapy in studies demonstrating outcome benefits for other antihypertensive agents. However, current evidence suggests that low-dose thiazides are not as effective as an ACE inhibitor (ASCOT) or a calcium channel blocker (ACCOMPLISH) when used as second-line add-on therapy. Compelling indications include the elderly, isolated systolic hypertension, heart failure and secondary stroke prevention. Although a history of gout is a compelling contraindication, thiazide or thiazide-like diuretics may sometimes be necessary to control blood pressure in people with gout, ideally in combination with allopurinol.

In the absence of a compelling indication for another drug or contraindication to a diuretic, thiazides and thiazide-like drugs should be used as recommended in the NICE/BHS algorithm.

- **step 1** option in people aged 55 years or older or of Afro-Caribbean descent
- **step 2** option with an ACE inhibitor or angiotensin receptor blocker
- **step 3** therapy with an ACE inhibitor or angiotensin receptor blocker plus a calcium channel blocker
- **step 4** therapy option

NB: Caution is advised when using a thiazide or a thiazide-like diuretic in combination with a beta-blocker because of the high risk of diabetes particularly in people with impaired glucose tolerance, obesity, features of the metabolic syndrome, strong family history of diabetes or of South Asian or Afro-Caribbean descent.

