

DRUG CLASSES

THIAZIDE AND THIAZIDE-LIKE DIURETICS

These drugs have formed historically the cornerstone of the management of hypertension for several decades.

Examples

Thiazides

Bendroflumethiazide
Cyclopentiazide
Hydrochlorothiazide

Thiazide-like

Chlortalidone
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 are well absorbed orally, widely distributed and subject to a variable degree of hepatic metabolism. The effects 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

- Hyponatraemia due to increased urinary sodium excretion
- Hyperuricaemia due to interference with renal clearance of uric acid. **Risk of acute gout**
- Hyperglycaemia possibly related to hypokalaemia. **Risk of new onset diabetes with long-term use**
- Hypercalcaemia due to reduced renal clearance of calcium
- Erectile dysfunction by an unknown mechanism.
- Thrombocytopenia 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 is 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 regimen. Efforts should be made to avoid hypokalaemia; co-administration of a potassium-sparing diuretic is preferable to use of potassium chloride supplements. Where hypertension is complicated by chronic renal impairment (serum creatinine > 150 µmol/l; eGFR < 45), thiazide and thiazide-like 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 fixed dose 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. 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. If a diuretic treatment is to be initiated or changed, NICE/BHS guidelines recommend a thiazide-like diuretic, such as chlortalidone (12.5 – 25.0 mg once daily) or indapamide (1.5 mg modified release or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as

bendroflumethiazide or hydrochlorothiazide because RCT evidence of beneficial cardiovascular outcomes is available for thiazide-like drugs but not for low-dose thiazides. For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment unchanged. 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, 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 African descent if a calcium channel blocker is not suitable because of oedema or intolerance or evidence of heart failure or high risk of heart failure
- **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** if potassium >4.5 mmol/l option to use an increased dose of thiazide/thiazide like diuretic

NB: Caution is advised when using a thiazide or a thiazide-like diuretic in combination with a beta-blocker because of the risk of developing 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.

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