

Thiazide Diuretics



**SHEBA MEDICAL CENTER
INTERNAL MEDICINE DEPARTMENT
EDMUND DUFFY**

Introduction



- Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule. They act within 1 to 2 hours of oral administration and most have a duration of action of 12 to 24 hours; they are usually administered early in the day so that the diuresis does not interfere with sleep.
- In the management of hypertension a low dose of a thiazide, e.g. bendroflumethiazide 2.5mg daily, produces a maximal or near-maximal blood pressure lowering effect, with very little biochemical disturbance. Higher doses cause more marked changes in plasma potassium, sodium, uric acid, glucose and lipids, with little advantage in blood pressure control.

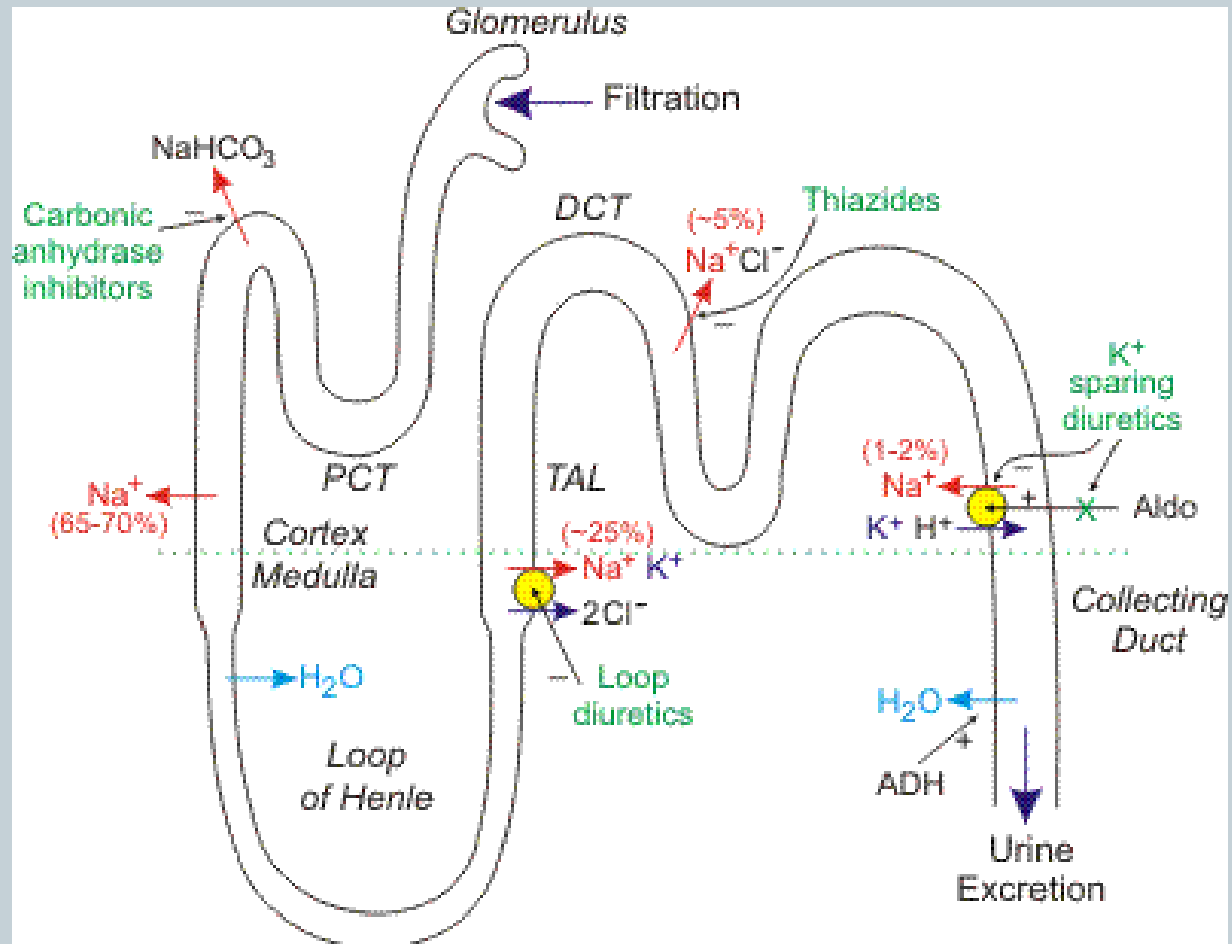


- **Bendroflumethiazide (Aprinox)**
- Chlortalidone (Hygroton)
- Indapamide (Indapamide, Natrilix, Ethibide XL)
- Metolazone (Metenix 5)
- Xipamide (Diurexan)

Mechanism of Action



- As a diuretic, bendroflumethiazide inhibits active chloride reabsorption at the early distal tubule via the Na-Cl co-transporter, resulting in an increase in the excretion of sodium, chloride and water.
- Thiazides like bendroflumethiazide also inhibit sodium ion transport across the renal tubular epithelium through binding to the thiazide sensitive sodium-chloride transporter. This results in an increase in potassium excretion via the sodium-potassium exchange mechanism.
- The anti-hypertensive mechanism of bendroflumethiazide is less well understood although it may be mediated through its action on carbonic anhydrases in the smooth muscle or through its action on the large-conductance calcium-activated potassium (KCa) channel, also found in the smooth muscle.



Indications



- To relieve oedema due to chronic heart failure
- In lower doses, to reduce blood pressure

Adverse Effects



- Mild gastro-intestinal disturbances
- Postural hypotension
- Altered plasma-lipid concentrations
- Metabolic and electrolyte disturbances
 - Incl. hypokalaemia, hyponatraemia, hypomagnesaemia, hypercalcaemia, hyperglycaemia, hypochloraemic alkalosis, hyperuricaemia and gout.
- Less common side-effects
 - Blood disorders
 - ✦ Such as agranulocytosis, leucopenia and thrombocytopenia, and impotence
 - Pancreatitis, intrahepatic cholestasis, cardiac arrhythmias, headache, dizziness

Interactions



- Hypertension may occur when used in combination with ACE inhibitors
- Patients taking carbamazepine (anti-convulsant) may experience symptomatic hyponatraemia with thiazide use.
- Corticosteroids may have a synergistic effect on potassium levels, resulting in hypokalaemia.
- Concomitant use of cholestyramine may result in drug binding.
 - Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolaemia who do not respond adequately to diet



- Decreased clearance of lithium (mood stabilizer) may result in an increased risk of lithium toxicity
- There is a potential for digitalis/digoxin (anti-arrhythmic) toxicity due to a hypokalaemia-induced proarrhythmic state
- Methotrexate used in combination with thiazides may result in myelosuppression.
- Concomitant use of NSAIDs may result in decreased diuretic effectiveness and increased potassium levels secondary to decreased synthesis of renal prostaglandins.
- Propranolol may exacerbate hyperglycaemia and hypertriglyceridaemia.

Cautions



- **Potassium loss**

- Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equivalent dose of a loop diuretic.
- Hypokalaemia is dangerous in severe cardiovascular disease and in patients also being treated with cardiac glycosides (e.g. digoxin). Often, the use of potassium-sparing diuretics avoids the need to take potassium supplements
- In hepatic failure, hypokalaemia caused by diuretics can precipitate encephalopathy, particularly in alcoholic cirrhosis; diuretics can also increase the risk of hypomagnesaemia in alcoholic cirrhosis, leading to arrhythmias. Spironolactone is chosen for oedema arising from cirrhosis of the liver.
- Potassium supplements or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension



- Thiazides can exacerbate diabetes, gout and SLE.
- Electrolytes should be monitored, particularly with high doses, long-term use, or in renal impairment.
- Thiazides should also be used with caution in nephrotic syndrome (kidney disease with proteinuria, hypoalbuminaemia and oedema), hyperaldosteronism and malnourishment.

Contraindications



- Refractory hypokalaemia, hyponatraemia and hypercalcaemia (unresponsive to a given treatment)
- Symptomatic hyperuricaemia
- Addison's disease (adrenal insufficiency)

Adjustments in Special Circumstances



- **Elderly**

- Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs and support stockings)

- **Hepatic impairment**

- Should be used with caution in mild to moderate impairment and avoided in severe liver disease.
- Hypokalaemia may precipitate coma, although hypokalaemia can be prevented by using a potassium-sparing diuretic.
- There is an increased risk of hypomagnesaemia in alcoholic cirrhosis



- **Renal impairment**

- Ineffective if eGFR is less than 30 and should be avoided; metolazone remains effective but with a risk of excessive diuresis

- **Pregnancy**

- Should not be used to treat gestational hypertension.
- They may cause neonatal thrombocytopaenia, bone marrow suppression, jaundice, electrolyte disturbances and hypoglycaemia' placental perfusion may also be reduced. Stimulation of labour, uterine inertia, and meconium staining have also been reported.

- **Breast-feeding**

- Amount present in milk is too small to be harmful; large doses may suppress lactation.

Prescribing



- Oedema

- PO

- ✦ Initially 5-10mg daily in the morning or on alternate days
- ✦ Maintenance 5-10mg 1-3 times weekly

- Hypertension

- PO

- ✦ 2.5mg daily in the morning