

# Diuretics

## Contents:

### (A) Types

1. High ceiling loop diuretics
2. Thiazides
3. Carbonic Anhydrase Inhibitors
4. Digitalis
5. Potassium-sparing diuretics
6. Calcium-sparing diuretics
7. Osmotic diuretics
8. Low ceiling diuretics

### (B) Uses

### (C) Mechanism of action

### (D) Adverse effects

## (A) Types

### *1) High ceiling loop diuretics*

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High ceiling diuretics are diuretics that may cause a substantial diuresis – up to 20% of the filtered load of NaCl and water. This is huge when compared to normal renal sodium reabsorption which leaves only ~0.4% of filtered sodium in the urine.

Loop diuretics, such as **furosemide**, inhibit the body's ability to reabsorb sodium at the ascending loop in the kidney which leads to a retention of water in the urine as water normally follows sodium back into the extracellular fluid (ECF).

#### Examples :

- furosemide
- bumetanide
- ethacrynic acid
- furosemide
- torsemide

#### Adverse effects

The most common adverse drug reactions include: hyponatremia, hypokalemia, hypomagnesemia, dehydration, hyperuricemia, gout, dizziness, postural hypotension, syncope,

Infrequent effects include: dyslipidemia, increased serum creatinine concentration, hypocalcemia, rash.

Ototoxicity (damage to the ear) is a serious, but rare. This may be limited to tinnitus and vertigo, but may result in deafness in serious cases.

Loop diuretics may also precipitate renal failure in patients concomitantly taking an NSAID and an ACE inhibitor -- the so-called "triple whammy" effect

## 2) Thiazides & Thiazides Like Diuretics

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Thiazide is a term used to describe a type of molecule and a class of diuretics often used to treat hypertension (high blood pressure) and edema (such as that caused by heart, liver, or kidney disease).

They work by inhibiting reabsorption of sodium (Na<sup>+</sup>) and chloride (Cl<sup>-</sup>) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na<sup>+</sup>-Cl<sup>-</sup> symporter. Thiazides also cause loss of potassium and an increase in serum uric acid.

### Thiazide diuretics:

- acetazolamide
- hydrochlorothiazide and chlorothiazide
- bendroflumethiazide

### Thiazide-like diuretics:

- indapamide
- chlorthalidone
- metolazone

### Clinically used in the following indications:

- edema associated with heart failure, hepatic cirrhosis, renal impairment, nephrotic syndrome
- hypertension
- adjunct in cerebral/pulmonary edema where rapid diuresis is required (IV injection)

They are also sometimes used in the management of severe hypercalcemia in combination with adequate rehydration

### Primary uses:

Thiazides are often used to treat hypertension, although they are also used to treat congestive heart failure and symptomatic edema. They are the recommended first-line treatment in the US as the first choice of treatment for cases of uncomplicated hypertension when pharmacotherapy is indicated, they have been replaced by ACE inhibitors in Australia due to their propensity to increase risk of diabetes mellitus type 2.

When administered acutely thiazides lower blood pressure by causing diuresis, a fall in plasma volume and a reduction in cardiac output. However, after chronic use thiazides cause a reduction in blood pressure by lowering peripheral resistance (i.e. vasodilation). The mechanism of this effect is uncertain but it may involve effects on 'whole body' or

renal autoregulation, or direct vasodilator actions either through inhibition of carbonic anhydrase or by desensitizing the vascular smooth muscle cells to the rise in intracellular calcium induced by norepinephrine.

### **Side effects:**

include hypokalemia, increased serum cholesterol, triglyceride, impaired glucose tolerance, diabetes mellitus and impotence. The side effect of hypokalemia has motivated combining thiazides with potassium chloride supplements, potassium sparing diuretics (e.g., with amiloride in co-amiloride) and with the newer ACE inhibitors, which also lower blood pressure but cause hyperkalemia as a side effect.

Long-term usage of thiazides is also linked to increased levels of homocysteine, a toxic amino acid byproduct that has been associated with atherosclerosis.

**Breast milk:** Thiazides pass through breast milk, and in some cases, decrease the flow of breast milk. There is no specific information regarding the use of thiazides in children, but it is still advised that mothers avoid using thiazides during the first month of breast feeding.

### **Contraindications:**

Thiazides reduce the clearance of uric acid and are therefore to be used with caution in patients with gout or hyperuricemia.

Thiazides can decrease placental perfusion and adversely affect the fetus so should be avoided in pregnancy.

## ***3) Potassium-sparing diuretics***

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Potassium-sparing diuretics are diuretic drugs that do not promote the secretion of potassium into the urine, They are used as adjunctive therapy, together with other drugs, in the treatment of hypertension and management of congestive heart failure.

### **Examples:**

#### **Epithelial sodium channel blockers:**

- Amiloride
- Triamterene

#### **Aldosterone antagonists:**

- Spironolactone
- Eplerenone

Potassium-sparing diuretics are generally used in combination with other diuretic drugs (e.g. loop diuretics) that would otherwise tend to lower the potassium levels to potentially dangerous low levels (hypokalemia). The combination therefore helps maintain a normal reference range for potassium (3.5 - 5.1 mmol/L).

**Adverse effects:**

On their own this group of drugs may raise potassium levels beyond the normal range, termed hyperkalemia, which risks potentially fatal arrhythmias.

**Mechanism of action:**

The potassium-sparing diuretics are competitive antagonists that compete with aldosterone for intracellular cytoplasmic receptor sites, or by directly blocking sodium channels (specifically ENaC by amiloride (ENaC is Epithelial Sodium Channel))

## 4) Carbonic Anhydrase Inhibitors

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Carbonic anhydrase inhibitors inhibit the enzyme carbonic anhydrase which is found in the proximal convoluted tubule. This results in several effects including bicarbonate retention in the urine, potassium retention in urine and decreased sodium absorption. Drugs in this class include acetazolamide and methazolamide.

Carbonic anhydrase inhibitors are a class of pharmaceuticals that suppress the activity of carbonic anhydrase. Their clinical use has been established as antiglaucoma agents, diuretics, antiepileptics, in the management of mountain sickness, gastric and duodenal ulcers, neurological disorders, or osteoporosis.

**Types:**

- **Acetazolamide** is an inhibitor of carbonic anhydrase. It is used for glaucoma, epilepsy (rarely), benign intracranial hypertension, and altitude sickness. It can act as a mild diuretic by reducing NaCl and bicarbonate reabsorption in the proximal tubule. However, the distal segment partially compensates for the sodium loss, and the bicarbonaturia will produce a metabolic acidosis, further reducing the effect.

- **Methazolamide** is also a carbonic anhydrase inhibitor. It has a longer elimination half-life than acetazolamide and is less associated with adverse effects to the kidney.

- **Dorzolamide** (a sulfonamide) and topical carbonic anhydrase II inhibitor. It is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension and who are insufficiently responsive to beta-blockers. Inhibition of carbonic anhydrase II in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

## 5) Digitalis

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Digitalis increase output of urine by increasing cardiac output and increased circulation through kidney. Digitalis has a diuretic effect on heart failure patients due to cardiac edema.

## 6) Calcium-sparing diuretics

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The term "calcium-sparing diuretic" is sometimes used to identify agents that result in a relatively low rate of excretion of calcium.

The reduced concentration of calcium in the urine can lead to an increased rate of calcium in serum. The sparing effect on calcium can be beneficial in hypocalcemia, or unwanted in hypercalcemia.

The thiazides and potassium-sparing diuretics are considered to be calcium-sparing diuretics.

- The thiazides cause a net decrease in calcium lost in urine.
- The potassium-sparing diuretics cause a net increase in calcium lost in urine, but the increase is much smaller than the increase associated with other diuretic classes.

## 7) Osmotic diuretics

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Compounds such as mannitol are filtered in the glomerulus, but cannot be reabsorbed. Their presence leads to an increase in the osmolarity of the filtrate. To maintain osmotic balance, water is retained in the urine.

Glucose, like mannitol, is a sugar that can behave as an osmotic diuretic. Unlike mannitol, glucose is commonly found in the blood. However, in certain conditions such as diabetes mellitus, the concentration of glucose in the blood (hyperglycemia) exceeds the maximum reabsorption capacity of the kidney. When this happens, glucose remains in the filtrate, leading to the osmotic retention of water in the urine. Glucosuria causes a loss of hypotonic water and Na<sup>+</sup> leading to a hypertonic state with signs of volume depletion such as: dry mucosa, hypotension, tachycardia, and decreased turgor of the skin. Use of some drugs, especially stimulants may also increase blood glucose and thus increase urination.

## 8) Osmotic diuretics

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The term "low ceiling diuretic" is used to indicate that a diuretic has a rapidly flattening dose effect curve (in contrast to "high ceiling", where the relationship is close to linear). It refers to a pharmacological profile, not a chemical structure. However, there are certain classes of diuretic which usually fall into this category, such as the thiazides.

# (B) Uses

In medicine, diuretics are used to treat heart failure, liver cirrhosis, hypertension and certain kidney diseases. Some diuretics, such as acetazolamide, help to make the urine more alkaline and are helpful in increasing excretion of substances such as aspirin in cases of overdose or poisoning.

The antihypertensive actions of some diuretics (thiazides and loop diuretics in particular) are independent of their diuretic effect. That is, the reduction in blood pressure is not due to decreased blood volume resulting from increased urine production, but occurs through other mechanisms and at lower doses than that required to produce diuresis. **Indapamide** was specifically designed with this in mind, and **has a larger therapeutic window for hypertension (without pronounced diuresis)** than most other diuretics.

## (C) Mechanism of action

Classification of common diuretics and their mechanisms of action:

	Examples	Mechanism
-----	Ethanol, Water	inhibits vasopressin secretion
Acidifying salts	CaCl <sub>2</sub> , NH <sub>4</sub> Cl	Arginine vasopressin receptor 2 antagonists
Aquaretics	Goldenrod, Juniper	Increases blood flow in kidneys
Na-H exchanger antagonists	dopamine	promote Na <sup>+</sup> excretion
Carbonic anhydrase inhibitors	acetazolamide, dorzolamide	inhibit H <sup>+</sup> secretion, resultant promotion of Na <sup>+</sup> and K <sup>+</sup> excretion
Loop diuretics	bumetanide, ethacrynic acid, furosemide, torsemide	inhibit the Na-K-2Cl symporter
Osmotic diuretics	glucose (especially in uncontrolled diabetes), mannitol	promote osmotic diuresis
Potassium-sparing diuretics	amiloride, spironolactone, triamterene, potassium canrenoate.	inhibition of Na <sup>+</sup> /K <sup>+</sup> exchanger: Spironolactone inhibits aldosterone action, Amiloride inhibits epithelial sodium channels
Thiazides	bendroflumethiazide, hydrochlorothiazide	inhibit reabsorption by Na <sup>+</sup> /Cl <sup>-</sup> symporter
Xanthines	caffeine, theophylline, theobromine	inhibit reabsorption of Na <sup>+</sup> , increase glomerular filtration rate

## (D) Adverse effects

The main adverse effects of diuretics are hypovolemia, hypokalemia, hyperkalemia, hyponatremia, metabolic alkalosis, metabolic acidosis and hyperuricemia

Adverse effect	Diuretics	Symptoms
<b>Hypovolemia</b>	<ul style="list-style-type: none"> <li>- loop diuretics</li> <li>- thiazides</li> </ul>	<ul style="list-style-type: none"> <li>- lassitude</li> <li>- thirst</li> <li>- muscle cramps</li> <li>- hypotension</li> </ul>
<b>hypokalemia</b>	<ul style="list-style-type: none"> <li>- acetazolamides</li> <li>- loop diuretics</li> <li>- thiazides</li> </ul>	<ul style="list-style-type: none"> <li>- muscle weakness</li> <li>- paralysis</li> <li>- arrhythmia</li> </ul>

<b>Hyperkalemia</b>	- amilorides - triamterenes - spironolactone	- arrhythmia - muscle cramps - paralysis
<b>hyponatremia</b>	- thiazides - furosemides	• CNS symptoms - Coma
<b>Adverse effect</b>	<b>Diuretics</b>	<b>Symptoms</b>
<b>metabolic alkalosis</b>	- loop diuretics - thiazides	- arrhythmia - CNS symptoms
<b>metabolic acidosis</b>	- acetazolamides - amilorides - triamterene	- Kussmaul respirations - muscle weakness - neurological symptoms <ul style="list-style-type: none"> <li>• lethargy</li> <li>• coma</li> <li>• seizures</li> <li>• stupor</li> </ul>
<b>hypercalcemia</b>	thiazides	- Gout, tissue calcification - fatigue, depression - confusion, anorexia - nausea, vomiting - constipation, pancreatitis - increased urination
<b>hyperuricemia</b>	- thiazides - loop diuretics	- gout

## Diuretics As Antihypertensive Agents

### Bumetanide

**Bumetanide** (Trade name Bumex) is a loop diuretic of the sulfamyl category to treat heart failure. It is often used in patients in whom high doses of furosemide are ineffective.

The main difference between the two substances is in bioavailability and pharmacodynamic potency. Furosemide is incompletely absorbed in the intestine (60%), and there is substantial inter- and intraindividual differences in bioavailability (range 10-90%). Bumetanide is completely absorbed (80%), and the absorption is not altered when it is taken with food. It is said to be a more predictable diuretic, meaning that the predictable absorption is reflected in a more predictable effect.

Bumetanide is 40 times more potent than furosemide (for patients with normal renal function).

On October 24, 2008, ESPN reported a number of sport players were being suspended under the steroid policy as a result of taking Bumetanide. The drug is often used for weight loss, but also to mask other drugs or steroids by helping to dilute the contents of the user's urine.

# Etacrynic acid

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Etacrynic acid or ethacrynic acid, trade name Edecrin, is a loop diuretic used to treat high blood pressure and the swelling caused by diseases like congestive heart failure, liver failure, and kidney failure.

Unlike the other loop diuretics, etacrynic acid is not a sulfonamide and thus, its use is not contraindicated in those with sulfa allergies.

## Administration

Ethacrynic acid is sold in 25 mg and 50 mg tablets for oral use. The sodium salt (ethacrynate sodium) can also be given intravenously.

## Adverse effects

As a diuretic, etacrynic acid can cause frequent urination, but this usually resolves after taking the drug for a few weeks. Etacrynic acid can also cause low potassium levels, which may manifest as muscle cramps or weakness. It has also been known to cause reversible or permanent hearing loss (ototoxicity) and liver damage. On oral administration, it produces diarrhea; intestinal bleeding may occur at higher doses.

## Mechanism of action

Etacrynic acid acts by inhibiting sodium-potassium-chloride cotransport in the ascending loop of Henle. Loss of potassium ions is less marked but chances of hypochloremic alkalosis are greater. The dose response curve of ethacrynic acid is steeper than that of furosemide and, in general, it is less manageable; dose range is 50-150mg.

Ethacrynic acid and its glutathione-adduct are potent inhibitors of glutathione S-transferase family members, which are enzymes involved in xenobiotic metabolism.

# Furosemide

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Furosemide or frusemide is a loop diuretic used in the treatment of congestive heart failure and edema. It is most commonly marketed by Sanofi-Aventis under the brand name Lasix. It has also been used to prevent thoroughbred and standardbred race horses from bleeding through the nose during races.

## Mechanism of action

Like other loop diuretics, furosemide acts by inhibiting the Na-K-2Cl symporter in the thick ascending limb of the loop of Henle. The action on the distal tubules is independent of any inhibitory effect on carbonic anhydrase or aldosterone.

By inhibiting the transporter, the loop diuretics reduce the reabsorption of NaCl and also diminish the lumen-positive potential that derives from K<sup>+</sup> recycling. This electrical potential normally drives divalent cation reabsorption in the loop, and by reducing this potential loop diuretics cause an increase in Mg<sup>2+</sup> and Ca<sup>2+</sup> excretion. Prolonged use can cause

significant hypomagnesemia in some patients. Since  $\text{Ca}^{2+}$  is actively reabsorbed in the distal convoluted tubule, loop diuretics do not generally cause hypocalcemia.

## Clinical use in humans

Furosemide, as a loop diuretic, is principally used in the following indications:

- Edema associated with heart failure, hepatic cirrhosis, renal impairment, nephrotic syndrome
- Hypertension
- Adjunct in cerebral/pulmonary edema where rapid diuresis is required (IV injection)

It is also sometimes used in the management of severe hypercalcemia in combination with adequate rehydration

The tendency, as for all loop diuretics, to cause low potassium levels (hypokalemia) has given rise to combination products, either with potassium itself (e.g. Lasix-K) or with the potassium sparing diuretic of amiloride (Co-amilofruse).

## Brand names

Aisemide, Apo-Furosemide, Beronald, Desdemin, Discoid, Diural, Diurapid, Dryptal, Durafurid, Errolon, Eutensin, Flusapex, Frusetic, Frusid, Fulsix, Fuluvamide, Furesis, Furix, Furo-Puren, Furosedon, Hydro-rapid, Impugan, Katlex, Lasilix, Lasix, Lodix, Lowpston, Macasirool, Mirfat, Nicorol, Odemase, Oedemex, Profemin, Rosemide, Rusyde, Salix, Trofurit, Uremide, Urex, Frudix, Fusid.frusone

The name Lasix is derived from the phrase "lasts six (hours)" — referring to its duration of action, Intravenous and oral lasix lasts two to four hours.

## Precautions and side-effects

As many diuretics, it can cause dehydration and electrolyte imbalance, including loss of potassium, calcium, sodium, and magnesium.

Excessive use of Furosemide will most likely lead to a metabolic alkalosis due to hypochloremia and hypokalemia. The drug should therefore not be used with that are dehydrated or experiencing kidney failure. It should be used with caution incase liver problems or electrolyte abnormalities. Overdose may lead to dehydration, change in drinking patterns and urination, seizures, GI problems, kidney damage, lethargy, collapse, and coma.

Furosemide should be used with caution when combined with corticosteroids (as this increases the risk of electrolyte imbalance), aminoglycoside antibiotics (increases risk of kidney or ear damage), and trimethoprim sulfa (causes decreased platelet count). It may also cause interactions with anesthetics, and it decreases the kidney's ability to excrete aspirin, so dosages will need to be adjusted if combined with that drug.

Furosemide may cause digoxin toxicity due to hypokalemia.

The drug is best not used during pregnancy or in a lactating mare, as it has been shown to be passed through the placenta and milk.

## Drug Interactions

- Furosemide has potential interactions with the following medications:
- Aminoglycoside antibiotics such as Gentamicin

- Aspirin and other salicylates
- Other diuretics (e.g. ethacrynic acid, hydrochlorothiazide)
- Indomethacin
- Lithium
- Synergistic effects with other antihypertensives (e.g. Doxazosin)
- Sucralfate

## Torsemide

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Torsemide or torsemide is a pyridine-sulfonyl urea type loop diuretic mainly used in the management of **edema\*\*** associated with **congestive heart failure**. It is also used at low doses for the management of hypertension. It is marketed under the brand name **Demadex**.

Compared to other loop diuretics, torsemide has a more prolonged diuretic effect than equipotent doses of furosemide and relatively decreased potassium-loss. There is no evidence of torsemide-induced ototoxicity demonstrated in humans

**Edema** (American English) or **oedema** (British English; "swelling"), formerly known as dropsy or hydropsy, is an abnormal accumulation of fluid beneath the skin or in one or more cavities of the body.

**Examples of edema in specific organs:**

**Cerebral edema**, **Pulmonary edema**, **lymphedema**, Edema may also be found in the **cornea** of the eye with glaucoma, Another cutaneous form of edema is **myxedema**.

## Hydrochlorothiazide

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Hydrochlorothiazide, abbreviated HCTZ, HCT, or HZT, is a first line diuretic drug of the thiazide class that acts by inhibiting the kidneys' ability to retain water. This reduces the volume of the blood, decreasing blood return to the heart and thus cardiac output and, by other mechanisms, is believed to lower peripheral vascular resistance.

Hydrochlorothiazide is sold both as a generic drug and under a large number of brand names, including Apo-Hydro, Aquazide H, Dichlotride, Hydrodiuril, HydroSaluric, Microzide, Esidrex, and Oretic.

Hydrochlorothiazide is also used in combination with many popular drugs used to treat hypertension such as Diovan HCT, Zestoretic, Benicar HCT, Atacand HCT, and Lotensin HCT and others.

### Mechanism of action

Hydrochlorothiazide belongs to the thiazide class of diuretics, acting on the kidneys to reduce sodium (Na) reabsorption in the distal convoluted tubule. The major site of action in the nephron appears on an electroneutral Na<sup>+</sup>-Cl<sup>-</sup> co-transporter by competing for the chloride site on the transporter. By impairing Na transport in the distal convoluted tubule, hydrochlorothiazide induces a natriuresis and concomitant water loss. Thiazides increase the reabsorption of calcium in this segment in a manner unrelated to sodium transport.

## Indications

HCTZ is often used in the treatment of hypertension, congestive heart failure, symptomatic edema and the prevention of kidney stones. It is effective for nephrogenic diabetes insipidus and is also sometimes used for hypercalciuria, Dent's disease and Ménière's disease, For diabetes insipidus, the effect of thiazide diuretics is presumably mediated by a hypovolemia-induced increase in proximal sodium and water reabsorption, thereby diminishing water delivery to the ADH-sensitive sites in the collecting tubules and reducing the urine output.

Hypokalemia, an occasional side effect, can be usually prevented by potassium supplements or by combining hydrochlorothiazide with a potassium-sparing diuretic.

Thiazides are also used in the treatment of osteoporosis. Thiazides decrease mineral bone loss by promoting calcium retention in the kidney, and by directly stimulating osteoblast differentiation and bone mineral formation.

## Side effects

- Hypokalemia
- Hypomagnesemia
- Hyperuricemia and gout
- High blood sugar
- Hyperlipidemia
- Hypercalcemia
- Headache
- Nausea/vomiting
- Photosensitivity
- Weight Gain

# chlorothiazide

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Chlorothiazide sodium (Diuril) is a diuretic used within the hospital setting or for personal use to manage excess fluid associated with congestive heart failure. It is also used as an antihypertensive.

Most often taken in pill form, it is usually taken orally once or twice a day. In the ICU setting, chlorothiazide is given to diurese a patient in addition to furosemide (Lasix).

## Indications

Large amount of excess fluid including:

- Diagnosed congested heart failure
- Peripheral edema
- Rales / Rhonchi
- Hypertension

## Contraindications

- Renal failure or insufficiency
- Allergies to sulfa drugs

## Dose

- 500 mg–1 g once or twice a day, by mouth or through NG tube (reconstituted suspension)

- May also be given intravenously, and should be given first if given in combination with IV lasix since it potentiates the diuretic effect of furosemide.

#### Side effects

- Nausea / Vomiting
- Headache
- Dizziness
- Excess urine production
- Dehydration
- Hypoelectrolytemia (esp. hypokalemia / hypomagnesia)

## Bendroflumethiazide

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Bendroflumethiazide, formerly bendrofluazide, is a thiazide diuretic used to treat hypertension.

It is also a fairly cheap drug, made cheap through mass production. Normal pharmaceutical trade prices vary from £0.10 - £0.20 for a 28 calendar pack of Bendroflumethiazide 2.5 tablets. Bendroflumethiazide (bendrofluazide) is a thiazide diuretic which works by inhibiting sodium absorption at the beginning of the distal convoluted tubule (DCT). Potassium is lost as a result of more sodium reaching the collecting ducts. Bendroflumethiazide has a role in the treatment of mild heart failure although loop diuretics are better for reducing overload. The main use of bendroflumethiazide currently is in hypertension (part of the effect is due to vasodilation).

#### Common adverse effects

- dehydration
- postural hypotension
- hyponatraemia, hypokalaemia, hypercalcaemia
- gout
- impaired glucose tolerance
- impotence

#### Rare adverse effects

- thrombocytopenia
- agranulocytosis
- photosensitivity rash
- pancreatitis

## ● Indapamide

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Indapamide is a non-thiazide sulphonamide diuretic drug marketed by Servier, generally used in the treatment of hypertension, as well as decompensated cardiac failure. The US trade name for indapamide is Lozol. Indapamide is marketed as Natrilix outside of the US. Combination preparations with perindopril (an ACE inhibitor antihypertensive) are also available.

It is described as a thiazide-like diuretic.

## Indications

Hypertension and edema due to congestive heart failure. Indapamide has been proven in the HYVET trial to reduce stroke and all cause mortality when given with or without perindopril to people over the age of 80 for the treatment of hypertension.

## Contraindications

Indapamide is contraindicated in known hypersensitivity to sulfonamides, severe renal failure, hepatic encephalopathy or severe hepatic failure and hypokalemia (low blood potassium levels).

There is insufficient safety data to recommend indapamide use in pregnancy or breastfeeding.

## Interactions

Caution is advised in the combination of indapamide with lithium and nonantiarrhythmic drugs causing wave burst arrhythmia (astemizole, bepridil, IV erythromycin, halofantrine, pentamidine, sultopride, terfenadine, vincamine).

## Adverse effects

Commonly reported adverse events are hypokalemia (low potassium levels), fatigue, orthostatic hypotension (blood pressure decrease on standing up) and allergic manifestations.

## Overdosage

Symptoms of overdosage would be those associated with a diuretic effect: electrolyte disturbances, hypotension, and muscular weakness. Treatment should be symptomatic, directed at correcting the electrolyte abnormalities.

# ● Chlortalidone

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Chlortalidone or chlorthalidone is a diuretic drug used to treat hypertension, originally marketed as Hygroton in the USA. It is described as a thiazide diuretic (or, rather, a thiazide-like diuretic because it acts similarly to the thiazides but does not contain the benzothiadiazine molecular structure). Compared with other medications of the thiazide class, chlorthalidone has the longest duration of action, but a similar diuretic effect at maximal therapeutic doses. It is often used in the management of hypertension and edema.

Unlike loop diuretics, chlorthalidone efficacy is diminished in patients with certain renal diseases (e.g. Chronic Renal Disease). A recent clinical trial (ALLHAT) compared chlorthalidone to doxazosin in the treatment of high-risk hypertensive patients. In this study, only chlorthalidone significantly reduced the risk of combined cardiovascular disease events, especially heart failure, when compared with drugs such as doxazosin. Chlorthalidone was approved by the FDA in 1960. The ALLHAT study conclusions showed that there was no significant difference in all-cause mortality, fatal heart disease, or non-fatal myocardial infarction when chlorthalidone was compared with lisinopril or amlodipine but did show decrease rates of heart failure after 6 years when compared with amlodipine and decreased rates of cerebrovascular disease after 6 years when compared with lisinopril leading the study conclusions to say that thiazide-type diuretics are preferred first-step in antihypertensive therapy.

## Mechanism of action

Chlorthalidone increases the excretion of sodium, chloride, and water into the renal lumen by inhibiting sodium ion transport across the renal tubular epithelium. Its primary site of action is in the cortical diluting segment of the ascending limb of the loop of Henle. Thiazides and related compounds also decrease the glomerular filtration rate, which further reduces the drug's efficacy in patients with renal impairment (e.g. renal insufficiency). By increasing the delivery of sodium to the distal renal tubule, chlorthalidone indirectly increases potassium excretion via the sodium-potassium exchange mechanism (i.e. apical ROMK/Na channels coupled with basolateral NKATPases). This can result in hypokalemia and hypochloremia as well as a mild metabolic alkalosis; however, the diuretic efficacy of chlorthalidone is not affected by the acid-base balance of the patient being treated.

Initially, diuretics lower blood pressure by decreasing cardiac output and reducing plasma and extracellular fluid volume. Eventually, cardiac output returns to normal, and plasma and extracellular fluid volume return to slightly less than normal, but a reduction in peripheral vascular resistance is maintained, thus resulting in an overall lower blood pressure. The reduction in intravascular volume induces an elevation in plasma renin activity and aldosterone secretion, further contributing to the potassium loss associated with thiazide diuretic therapy.

## ● Metolazone

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Metolazone is a thiazide-like diuretic marketed under the brand names Zytanix from Zydus Cadila, Zaroxolyn, and Mykrox. It is primarily used to treat congestive heart failure and high blood pressure. Metolazone indirectly decreases the amount of water reabsorbed into the bloodstream by the kidney, so that blood volume decreases and urine volume increases. This lowers blood pressure and prevents excess fluid accumulation in heart failure. Metolazone is sometimes used together with loop diuretics such as furosemide or bumetanide, but these highly effective combinations can lead to dehydration and electrolyte abnormalities.

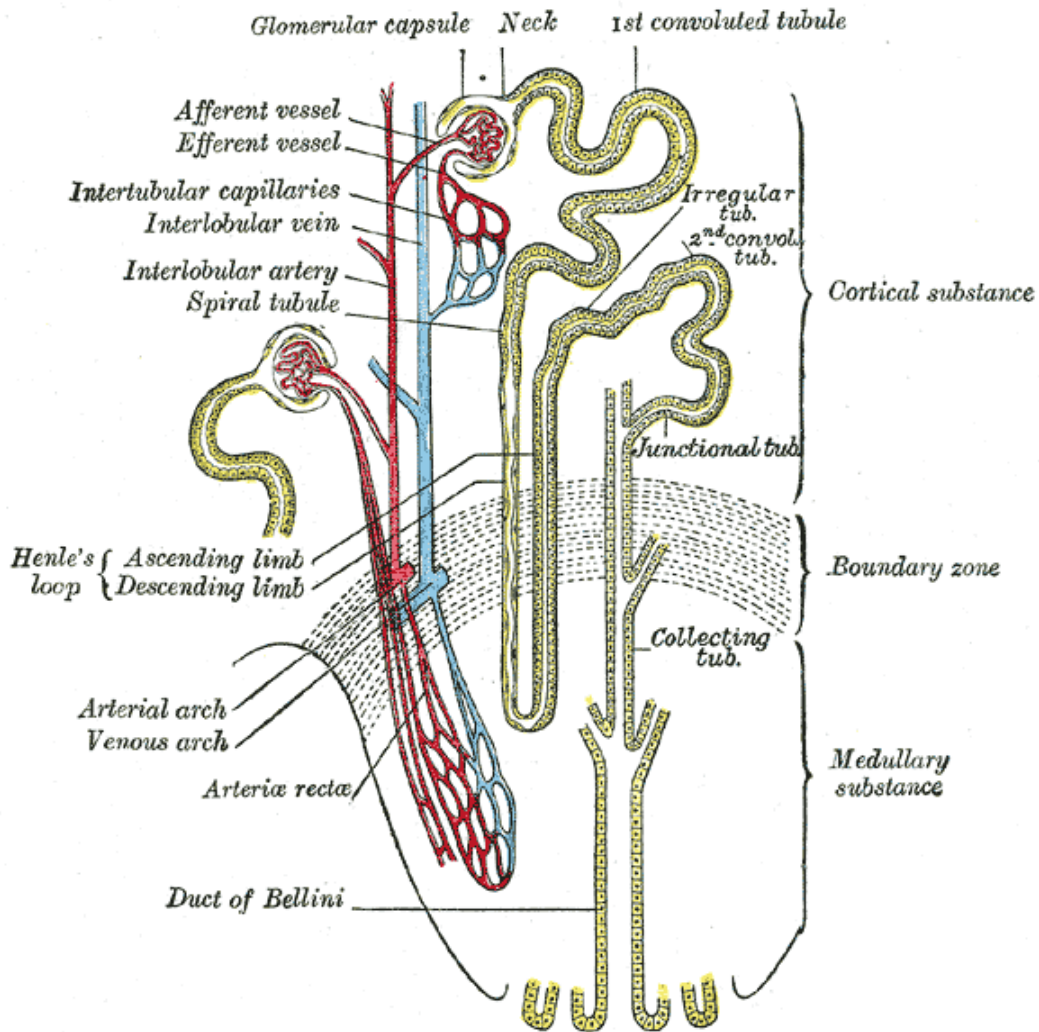
### **Mechanism of action**

The primary target of all thiazide diuretics, including metolazone, is the distal convoluted tubule, part of the nephron in the kidney, where they inhibit the sodium-chloride symporter.

In the kidney, blood is filtered into the lumen, or open space, of the nephron tubule. Whatever remains in the tubule will travel to the bladder as urine and eventually be excreted. The cells lining the tubule modify the fluid inside, absorbing some material and excreting others. One side of the cell (the apical side) faces the lumen; the opposite side (the basolateral side) faces the interstitial space near blood vessels. The other sides are tightly joined to neighboring cells.

As with other regions, tubule cells in the distal convoluted tubule possess the ATP-powered sodium-potassium antiporter (Na<sup>+</sup>/K<sup>+</sup>-ATPase), which uses energy from ATP to transfer three sodium ions out from the basolateral surface (toward blood vessels) while simultaneously transferring two potassium ions in. The distal convoluted tubule cells also possess a sodium-chloride symporter on the apical side, which passively allows one sodium ion and one chloride ion to diffuse together in from the lumen (where urine is forming) into the cell interior. As sodium is pumped out of the cell by the ATPase, its intracellular concentration falls, and additional sodium begins to diffuse in from the tubule lumen as replacement. The symporter requires chloride to be transported in as well. Water passively follows to maintain isotonicity; excess chloride and potassium passively diffuse out the cell through basolateral channels into the interstitial space, and water accompanies them. The water and chloride, as well as the sodium pumped out by the ATPase, will be absorbed into the bloodstream.

Metolazone and the other thiazide diuretics inhibit the function of the sodium-chloride symporter, preventing sodium and chloride, and therefore water too, from leaving the lumen to enter the tubule cell. As a result, water remains in the lumen and is excreted as urine, instead of being reabsorbed into the bloodstream. Since most of the sodium in the lumen has already been reabsorbed by the time the filtrate reaches the distal convoluted tubule, thiazide diuretics have limited effects on water balance and on electrolyte levels. Nevertheless, they can be associated with low sodium levels, volume depletion, and low blood pressure, among other adverse effects.



## Use

One of the primary uses of metolazone is for treating oedema (fluid retention) associated with congestive heart failure (CHF). In mild heart failure, metolazone or another diuretic may be used alone, or combined with other diuretics for moderate or severe heart failure. In addition to preventing fluid buildup, the use of metolazone may allow the patient to relax the amount of sodium restriction that is required. Although most thiazide diuretics lose their effectiveness in renal failure, metolazone remains active even when the glomerular filtration rate (GFR) is below 30–40 mL/min (moderate renal failure). This gives it a considerable advantage over other thiazide diuretics, since renal and heart failure often coexist and contribute to fluid retention.

Metolazone may also be used in renal (kidney) disease, such as chronic renal failure or the nephrotic syndrome. Chronic renal failure causes excess fluid retention that is often treated with diet adjustments and diuretics. Metolazone may be combined with other diuretics (typically loop diuretics) to treat diuretic resistance in CHF, chronic renal failure, and nephrotic syndrome. Metolazone and a loop diuretic will synergistically enhance diuresis over the use of either agent alone. Using this combination, diuretic effects will occur at two different segments of the nephron; namely, the loop diuretic will act at the loop of Henle, and metolazone will act at the distal convoluted tubule. Metolazone is frequently prescribed in addition to the loop diuretic. Metolazone may be used for edema caused by liver cirrhosis as well.

The other major use of metolazone is in treating hypertension (high blood pressure). Thiazide diuretics, though usually not metolazone, are very often used alone as first-line treatment for mild hypertension. They are also used in combination with other drugs for difficult-to-treat or more severe hypertension. "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7) recommends thiazide diuretics as the initial medication for treatment of hypertension. Hydrochlorothiazide is by far the most commonly used, as it is both better-studied and cheaper (about four times) than metolazone, although as mentioned above metolazone is used in patients with moderate renal failure.

## Toxicity

Since thiazide diuretics affect the transport of electrolytes and water in the kidney, they can be responsible for abnormalities of water balance and electrolyte levels. Removal of too much fluid can cause volume depletion and hypotension. Various electrolyte abnormalities may result, including hyponatremia (low sodium), hypokalemia (low potassium), hypochloremia (low chloride), hypomagnesemia (low magnesium), hypercalcemia (high calcium), and hyperuricemia (high uric acid). These may result in dizziness, headache, or heart arrhythmias (palpitations). Serious, though rare, side effects include aplastic anemia, pancreatitis, agranulocytosis, and angioedema. Metolazone, like other thiazide diuretics, may unmask latent diabetes mellitus or exacerbate gout, especially by interacting with medicines used to treat gout. In addition, thiazide diuretics, including metolazone, are sulfonamides; those with hypersensitivity to sulfonamides ("sulfa allergy") may also be allergic to metolazone.

## ● Amiloride

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Amiloride is a potassium-sparing diuretic, first approved for use in 1967 (then known as MK 870), used in the management of hypertension and congestive heart failure.

Amiloride is a guanidinium group containing pyrazine derivative.

## Mechanism of action

Amiloride works by directly blocking the epithelial sodium channel (ENaC) thereby inhibiting sodium reabsorption in the late distal convoluted tubules, connecting tubules, and collecting ducts in the kidneys (this mechanism is the same for triamterene). This promotes the loss of sodium and water from the body, but without depleting potassium. The drug is often used in conjunction with thiazide (e.g. co-amiloride) or loop diuretics (e.g. co-amilorfruse). Due to its potassium-sparing capacities, hyperkalemia (high blood potassium levels) are occasionally observed in patients taking amiloride. The risk is high in concurrent use of ACE inhibitors or spironolactone. Patients are also advised not to use potassium-containing salt replacements. Amiloride also carries the risk of developing an acidosis.

A fraction of the effects of amiloride is inhibition of cyclic GMP-gated cation channels in the inner medullary collecting duct.

Amiloride has a second action on the heart, blocking Na<sup>+</sup>/H<sup>+</sup> exchangers Sodium-hydrogen antiporter 1 or NHE-1. This minimizes reperfusion injury in ischemic attacks.

## ● Triamterene

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Triamterene (trade name Dyrenium) is a potassium-sparing diuretic used in combination with thiazide diuretics for the treatment of hypertension and edema.

### Mechanism of action

Triamterene directly blocks the epithelial sodium channel (ENaC) on the lumen side of the kidney collecting tubule. Other diuretics cause a decrease in the sodium concentration of the forming urine due to the entry of sodium into the cell via the ENaC, and the concomitant exit of potassium from the principal cell into the forming urine. Blocking ENaC prevents this from happening. Amiloride works in the same way. Sodium channel blockers directly inhibit the entry of sodium into the sodium channels.

### Side effects

Common side effects may include a depletion of sodium, folic acid and calcium, nausea, vomiting, diarrhea, headache, dizziness, fatigue, and dry mouth. Serious side effects may include heart palpitations, tingling/numbness, fever, chills, sore throat, rash, and back pain. Triamterene can also cause kidney stones through direct crystallization or by seeding calcium oxalate stones. Triamterene is best avoided in patients with chronic kidney disease due to the possibility of hyperkalemia. People using this drug should use salt substitute cautiously.

Triamterene may impart a blue fluorescent color to the urine.

### Caution with certain disease states

Diabetes: Use with caution in patients with prediabetes or diabetes mellitus as there may be a change in glucose control.

Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

Kidney stones: Use with caution in patients with kidney stones.

Use should be avoided if the creatinine clearance is less than 10 ml/minute.

### Use in Ménière's disease \*

While there is a lack of randomized controlled trials evaluating the use of triamterene in the treatment of Ménière's disease, the typical treatment is 37.5 mg of triamterene with 25 mg of hydrochlorothiazide 1-2 capsules daily.

\* Ménière's disease

Ménière's disease is a disorder of the inner ear that can affect hearing and balance to a varying degree. It is characterized by episodes of vertigo and tinnitus and progressive hearing loss, usually in one ear.

## • Spironolactone

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Spironolactone (marketed under the trade names Aldactone, Novo-Spiroton, Aldactazide, Spiractin, Spirotone, Verospiron or Berlactone) is a diuretic and is used as an antiandrogen.

It is a synthetic 17-lactone drug that is a renal competitive aldosterone antagonist in a class of pharmaceuticals called potassium-sparing diuretics, used primarily to treat heart failure, ascites in patients with liver disease, low-renin hypertension, hypokalemia, secondary hyperaldosteronism (such as occurs with hepatic cirrhosis), and Conn's syndrome (primary hyperaldosteronism). On its own, spironolactone is only a weak diuretic because its effects target the distal nephron (collecting tubule), where urine volume can only be slightly modified; but it can be combined with other diuretics to increase efficacy. About one person in one hundred with hypertension has elevated levels of aldosterone; in these persons, the antihypertensive effect of spironolactone may exceed that of complex combined regimens of other antihypertensives. Due to its antiandrogen effect, it can also be used to treat hirsutism, and is a common component in hormone therapy for male-to-female transsexual and transgender people. It is also used for treating hair loss and acne in women, and can be used as a topical medication for treatment of male baldness. It is commonly used to treat symptoms of polycystic ovary syndrome (PCOS) such as excess facial hair and acne. It can also cause gynecomastia in males and should never be given with potassium supplementation for fear of the development of hyperkalemia.

### **Mechanism of action**

Spironolactone inhibits the effect of aldosterone by competing for intracellular aldosterone receptors in the cortical collecting duct. This decreases the reabsorption of sodium and water, while decreasing the secretion of potassium. Spironolactone has a fairly slow onset of action, taking several days to develop, and, so, the effect diminishes slowly. This is because steroid pathways alter gene transcription, and it will take several days for the gene products to change (in this case the ENaC and ROMK channels will be decreased). Spironolactone has anti-androgen activity by binding to the androgen receptor and preventing it from interacting with dihydrotestosterone.

### **Adverse effects and interactions**

Spironolactone is associated with an increased risk of bleeding from the stomach and duodenum, but a causal relationship between the two has not been established. Because it also affects androgen receptors and other steroid receptors, it can cause gynecomastia, menstrual irregularities and testicular atrophy. Other side-effects include ataxia, erectile dysfunction, drowsiness, and rashes. A carcinogenic effect has been demonstrated in rats, see below. Spironolactone has been shown to be immunosuppressive in the treatment of sarcoidosis.

Spironolactone often increases serum potassium levels and can cause hyperkalemia, a very serious condition. Therefore, it is recommended that people using this drug avoid potassium supplements and salt substitutes containing potassium. Doctors usually recommend periodic screening of serum potassium levels and some patients may be advised to limit dietary consumption of potassium.

Research has also shown that spironolactone can interfere with the effectiveness of antidepressant treatment. The drug is actually (among its other receptor interactions) a mineralocorticoid (MR) antagonist, and has been found to reduce

the effectiveness of antidepressant drugs in the treatment of major depression, it is presumed by interfering with normalization of the hypothalamic-pituitary-adrenal axis in patients receiving antidepressant therapy.

### Carcinogenicity

Studies of spironolactone and the related compound potassium canrenoate (which, like spironolactone, metabolizes to canrenone) in rats for one- to two-year periods show an increase in carcinogenesis in the thyroid gland, testes, liver, breasts, and myelocytic leukocytes. Mammalian cells, depending on the presence of metabolic activation, show mixed results for mutagenicity in vitro. Doses relative to body weight were 10 to 150 mg per kg, which is ten to 500 times higher than normal doses for treating humans. In light of this research, Sandoz has recommended that unnecessary use of spironolactone be avoided.

### Other potential benefits

It has been suggested that spironolactone can reduce the risk of Alzheimer's disease. In one study, researchers observed a reduction in the risk of Alzheimer's specifically associated with potassium-sparing diuretics. Unpublished findings from other studies, including the Gothenberg Study have suggested that higher potassium levels may be associated with a lower risk of dementia.

## Antihypertensives: diuretics

<b>Sulfonamides (except Etacrynic acid)</b>	CA inhibitors (at PT)	Acetazolamide
	Loop (Na-K-Cl at AL)	Furosemide, Bumetanide, Torasemide, Etacrynic acid
	Thiazides (Na-Cl at DCT, Calcium-sparing)	Hydrochlorothiazide • Bendroflumethiazide • Hydroflumethiazide • Chlorothiazide • Polythiazide • Trichlormethiazide • Cyclopentiazide • Methyclothiazide • Cyclothiazide • Mebutizide
	Thiazide-likes (primarily DCT)	Quinethazone • Clopamide • Chlortalidone • Mefruside • Clofenamide • Metolazone • Meticrane • Xipamide • Indapamide • Clorexolone • Fenquizone
<b>Potassium-sparing</b>	ESC blockers	Amiloride • Triamterene • Benzamil
	Aldosterone antagonists	Spironolactone • Eplerenone • Potassium canrenoate • Canrenone
<b>Osmotic diuretics</b>	Mannitol • Urea	
<b>VAs (Vasopressin receptor antagonist)</b>	vaptans: Conivaptan • Mozavaptan • Satavaptan • Tolvaptan tetracyclines: Demeclocycline	
<b>Other</b>	mercurial diuretic (Mersalyl) • Theobromine • Cicletanine	

Only the thiazide and thiazide-like diuretics have good evidence of beneficial effects on important endpoints of hypertension, and hence, should usually be the first choice when selecting a diuretic to treat hypertension. The reason why thiazide-type diuretics are better than the others is (at least in part) thought to be because of their vasodilating properties.

Evaluation and Treatment of High Blood Pressure) recommends starting with a thiazide diuretic if single therapy is being initiated and another medication is not indicated. This is based on a slightly better outcome for chlortalidone in the ALLHAT study versus other anti-hypertensives and because thiazide diuretics are relatively cheap.

Despite thiazides being cheap, effective, and recommended as the best first-line drug for hypertension by many experts, they are not prescribed as often as some newer drugs. This is because they have been associated with increased risk of new-onset diabetes and as such are recommended for use in patients over 65 where the risk of new-onset diabetes is outweighed by the benefits of controlling systolic blood pressure.

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