Thiazide Diuretics

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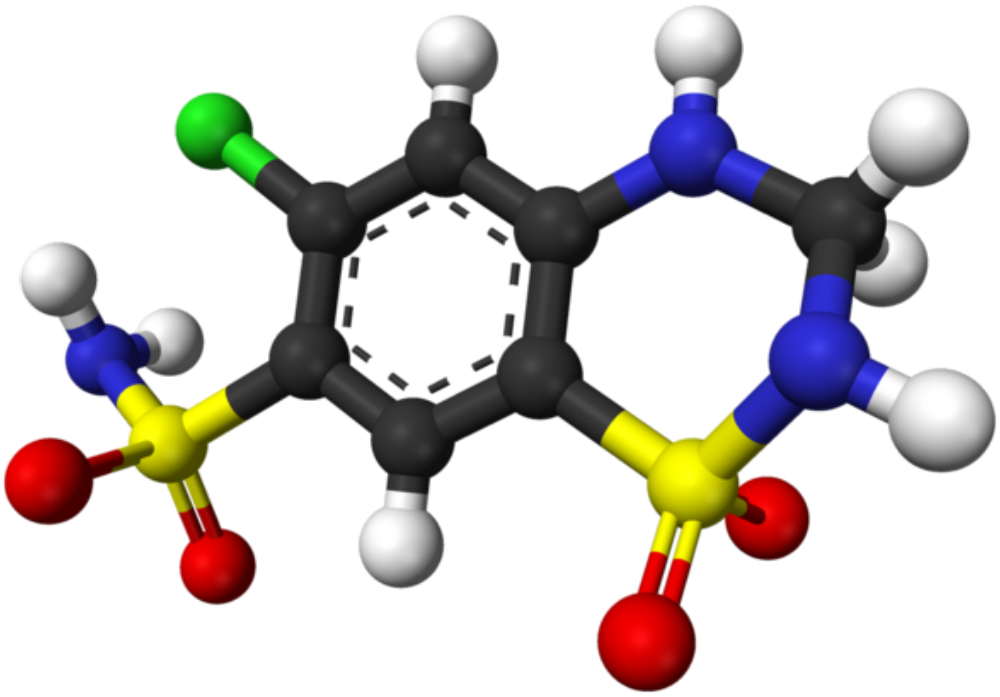
Thiazide diuretics are some of the most common diuretics currently in use. Their mechanism of action involves inhibition of the Na/Cl co-transporter channel in the proximal part of the distal convoluted tubule, leading to increased sodium and chloride secretion. Their effects on reducing peripheral vascular resistance further contribute to their antihypertensive properties, in addition to their ability to decrease effective blood volume. Besides hypertension, they are indicated for the treatment of heart failure exacerbation, hypercalciuria and diabetes insipidus. Important side effects include hypokalemia, hypercalcemia, hyponatremia, hyperglycemia, hyperuricemia, and hypomagnesemia.



Overview of Thiazide Diuretics

Thiazide diuretics are perhaps the most **commonly used diuretics**. They were designed as derivatives from **sulfonamides**, which acted as **carbonic anhydrase inhibitors**. They share a common **benzothiadiazine ring**, from which they derive their name. The most commonly used thiazides include chlorothiazide, hydrochlorothiazide and bemetizide. More recently, thiazide analogs were developed. They possess the same mechanism of action in the kidney, but not the basic structure of thiazides. These include chlorthalidone, metalozone and indapamide.

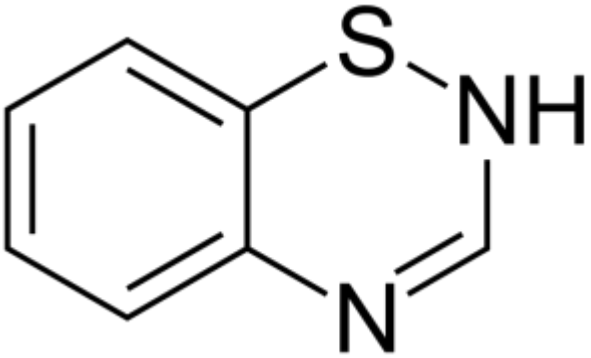


Image: Benzothiadiazine ring. By Lecturio

Thiazide diuretics are **medium efficacy diuretics** as compare to the loop diuretics (**higher efficacy diuretics**).

Among the thiazide diuretics, the most widely used drugs are:

Thiazides	Thiazide-like analogs
1. Chlorothiazide	1. Chlorthalidone
2. Chlorthalidone	2. Metalozone
3. Hydrochlorothiazide	3. Indapamide

Pharmacokinetics

Thiazide diuretics share many common pharmacokinetic properties. All of them can be **orally absorbed**, although chlorothiazide is the only compound that exhibits dose-dependent oral absorption. They are bound to plasma protein and are **actively excreted by the kidneys** through the organophosphate excretory system.

Elimination half-lives tend to be short, about 1–3 hours, although more recent studies suggest that in some cases they can reach more than 8–9 hours. The thiazides' **duration of action** varies. For example, chlorthalidone has t 1/2 of 40–50 hours. The duration of action of chlorthalidone is around 48 hours. Xipamide has a duration of action of only 5–8 hours.

Because of its low lipid solubility, **chlorothiazide** must be given in large doses. It is, however, **the only thiazide that can be administered through the IV route**.

Thiazide plasma levels rapidly peak after ingestion, approx. within 1 hour of PO intake and significantly bind with albumin in the serum. For example, chlorothiazide has a binding level with an albumin of 70 %. Thiazides do not undergo heavy metabolism, and some agents such as chlorothiazide are **excreted entirely unaffected in the urine**. **Probenecid**, a drug used as an anti-inflammatory agent, **decreases the rate of excretion** of thiazide diuretics.

Mechanisms of Action

Thiazide diuretics act by **decreasing the reabsorption of NaCl through the inhibition of Na^+/Cl^- co-transporter on the distal convoluted tubule**. The end result is an elevation in the concentration of NaCl in tubular fluid, without any disturbances of the acid-base balance.

An important property of thiazide diuretics is their **action on the luminal membrane**, which means they must be present in the **tubular fluid** to have any effect on the Na/Cl co-transporter. Thus, they must be excreted into the tubular fluid to be active, so **that a decrease in renal function makes thiazide diuretics much less effective**.

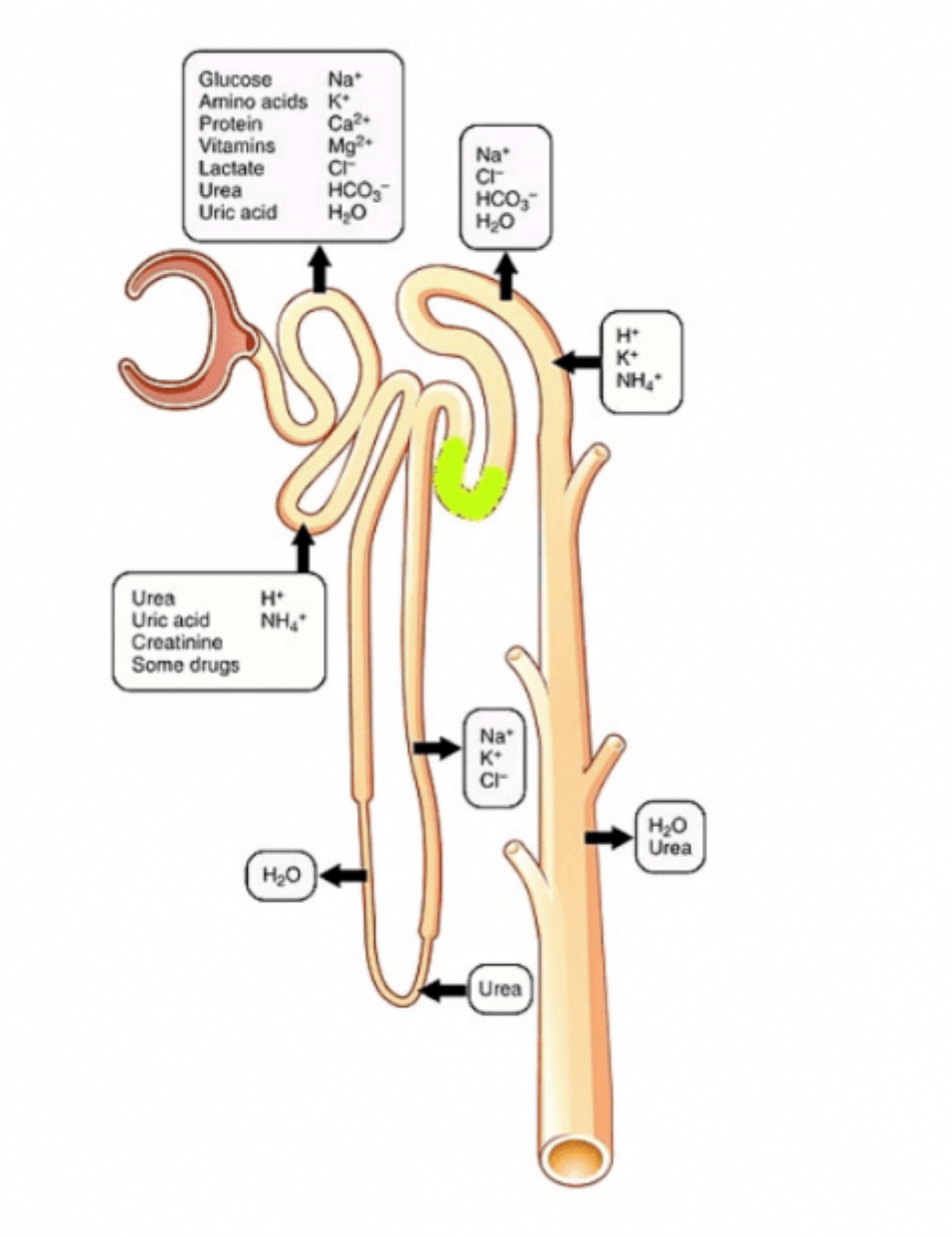


Image: Site of action (highlighted in green) of thiazide diuretics in a nephron. By OpenStax College, License: CC BY 3.0, modified by Lecturio

The net effects of the action of thiazide diuretics are the following:

Increase in NaCl excretion, resulting in hyperosmolar urine: This is **a unique property** to thiazide diuretics. Other diuretics are not likely to produce hyperosmolar urine. This effect is independent of the **acidity of the urine** and would not affect acid-base balance in the body.

Loss of Potassium: Second major effect of thiazide diuretics is a **decrease in K+ concentration**. This is due to the fact that tubular fluid arriving at the distal tubules is richer in sodium, leading to an increased exchange of potassium for sodium and resulting in continual loss of potassium ions. It is extremely important to continuously measure

potassium levels during thiazide treatments to avoid the development of **hypokalemia**.

Loss of Magnesium: The mechanism underlying loss of magnesium, or **magnesuria**, is not very well understood. This phenomenon entails the supplementation of magnesium in cases of chronic treatment with thiazide diuretics, particularly among the elderly.

Increase in calcium: The action of thiazide diuretics leads to a **decrease in urinary calcium excretion** and subsequent **elevations of blood calcium levels**. Unlike the loop diuretics, which increase calcium concentration in the urine, **thiazide diuretics increase calcium reabsorption**. The parathyroid hormone is thought to mediate this effect due to its action on the proximal renal tubule. **Thiazide-induced hypercalcemia** can have advantages as recent epidemiological studies have shown preservation of **bone mineral density** in the **hip and the spine** as well as a **decrease** in the **risk of hip fracture** in patients on chronic thiazide treatment.

Important: Thiazides decrease calcium excretion while loop diuretics increase it.
Reduced peripheral vascular resistance: Thiazide diuretics exert their **antihypertensive effects** by decreasing blood volume and cardiac output. Nonetheless, even after blood volume normalization, thiazide diuretics **decrease blood pressure** by reducing peripheral vascular resistance through relaxation of arteriolar smooth muscle.

Indications

Thiazide diuretics have many therapeutic uses that are summarized below:

Hypertension

Thiazides are historically one of **the most commonly used antihypertensive drugs** because they are inexpensive, are widely available, can be convenient to take and do not have severe side effects.

They **reduce** both **systolic and diastolic blood pressure** on a long term basis, particularly in mild and moderate cases of hypertension.

They are **quick to exert their antihypertensive effects,** and blood pressure can stabilize on the lower range after 3–7 days of intake. Their effect is indefinite because, even after blood volume normalizes, they relax arteriolar smooth muscle, leading to decreased peripheral vascular resistance and a decrease in blood pressure.

Patients can be followed on thiazides alone, although some cases would require the addition of another hypertensive, such as beta-blockers.

Thiazide diuretics are **first-line antihypertensive agents** in the US and Europe but are not in the UK or Australia due to increased diabetes mellitus type 2 risk. It is also important to note that the **actions of angiotensin-converting enzyme inhibitors (ACEi) are enhanced with the concurrent intake of thiazides**.

Important: Thiazides are preferred drugs in the hypertension over loop diuretics; furosemide is a **weaker hypertensive** than the thiazides.

Heart failure

Thiazides can be the first **choice in reducing volume overload** in cases of heart failure. If their effect is not strong enough to reduce symptoms, loop diuretics can be added.

Important: Loop diuretics are the preferred drugs in CHF as thiazides are ineffective sometimes and are used for maintenance in CHF.

Hypercalciuria

Thiazides inhibit calcium excretion, so they can be particularly effective in cases of **idiopathic hypercalciuria**. Their effects are especially beneficial for patients suffering from **calcium oxalate stones in the urinary tract**.

Diabetes Insipidus

Thiazide diuretics result in the formation of hyperosmolar urine and can be used as substitutes for antidiuretic hormone in the treatment of diabetes Inspidus.

Adverse Effects

Thiazide diuretics can disturb electrolyte balance in the body and lead to the following side effects:

Hypokalemia

Loss of potassium is the most common problem with the intake of thiazide diuretics. It is especially important in patients who are taking **digitalis** as it can predispose them to ventricular arrhythmias.

Repletion is usually initiated by an increased intake of fruits and vegetables rich in potassium such as bananas, prunes, lemons, and oranges. Nonetheless, **persistent hypokalemia** requires supplements with potassium salts.

Because **thiazide reduces effective blood volume**, the **renin-angiotensin-aldosterone system** is activated, leading to increased excretion of potassium and **exacerbating the hypokalemia**. This effect can be mitigated by spironolactone, which inhibits aldosterone and decreases potassium excretion, and triamterene, which acts directly on potassium channels.

Furthermore, low sodium diets can further serve to decrease potassium excretion due to a decrease in the sodium potassium exchange in the distal tubule.

Hyponatremia

The result of decreased effective blood volume from thiazide administration can lead to the **activation of Antidiuretic Hormone**, increased water retention and subsequent decrease in sodium concentration.

In addition, hyponatremia is also caused by the decreased diluting capacity of the kidneys and increased thirst caused by hypovolemia. This is a serious side effect that can be avoided by decreasing the drug dosage and water intake.

Hyperuricemia

Thiazide diuretics influence the action of the organic acid-excretory system leading to elevated uric acid serum levels. In individuals predisposed to **gout**, this can lead to deposition of insoluble uric acid crystals in the joints and subsequent full-blown gouty

attacks.

It is important to note here that **probenecid**, a common drug used in acute attacks of gout, can interfere with the excretion of thiazides, leading to further **elevation in uric acid levels** and exacerbation of the gout attacks.

Hypovolemia

It can lead to **orthostatic hypotension** or a feeling of light-headedness.

Hypercalcemia

It results because of the action of thiazide diuretics to inhibit calcium secretion.

Hyperglycemia

This side-effect manifests, particularly in **diabetic patients**. The mechanism of action involves inhibition of insulin secretion as well as glucose uptake in the tissues.

Hypersensitivity

Allergic reactions tend to be mild and are particularly prominent with those who are also allergic to sulfa drugs. More severe reactions are very rare and include: **interstitial nephritis, bone marrow suppression, dermatitis and necrotizing vasculitis.**

Less serious side effects include the following: **dizziness, blurred vision, loss of appetite, itching, indigestion, headache, and weakness**. They can also increase sensitivity to sunlight, and, similarly to other hypertensive drugs, they may cause **reversible sexual dysfunction**.

Contraindications

Thiazide diuretics are contraindicated in the following cases:

- Hypotension
- Allergy to sulfa drugs
- Gout
- Hypokalemia
- Renal failure
- Lithium treatment

In addition, **thiazides need to be avoided in pregnancy** because of a decrease in placental perfusion.

Precautions and Drug Interactions

The following drug interactions involving thiazides are considered significant:

- Angiotension converting enzyme inhibitors: **Hypotension.**
- Carbamezapine: **Symptomatic hyponatremia**. Carbamezapine is an important cause of hyponatremia.
- Corticosteroids: **Hypokalemia**.
- Lithium: **Lithium toxicity** due to decreased clearance.

- Digitalis: May lead to **digitalis toxicity** because of the decreased threshold of ventricular arrhythmias due to hypokalemia.
- Methotrexate: Myelosuppression. **Methotrexate** is an independent risk factor for bone marrow suppression.
- Non-steroidal anti-inflammatory drugs (NSAIDs): Lead to **decreased renal prostaglandin synthesis**, which inhibits the diuretic effects of thiazides and may lead to hypokalemia.

Other precautions: Thiazides should be **avoided in diabetic patients** because of worsening **hyperglycemia**. Extensive sun exposure should also be avoided due to increased sensitivity to sunlight. They **should not be taken during pregnancy** because they imperil blood perfusion to the placenta and may lead to **fetal abnormalities**.

Thiazide-like Analogs

These are a subset of compounds that do not possess the **characteristic thiazide structure**, but they have a similar mechanism of action and share an unsubstituted sulfonamide group. They include chlorthalidone, metalozone, and indapamide. Following are distinguishing characteristics for each:

Chlorthalidone: This compound has a very similar profile to hydrochlorothiazide. It is also characterized by **long duration of action (48 hours),** which makes it optimal for the treatment of hypertension as it can be dosed once a day.

Metalazone: Has increased potency relative to thiazides and **leads to sodium excretion even in severe renal failure**.

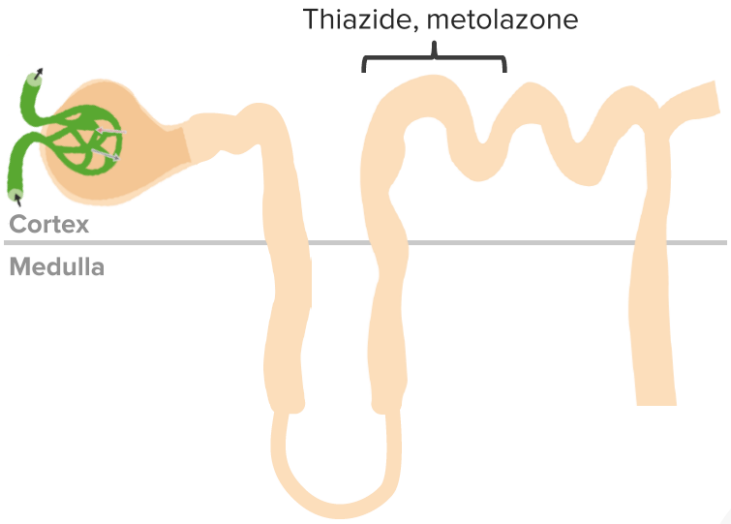


Image: Metolazone is given in acute situations. By Lecturio

Indapamide: Like chlorthalidone, it is also characterized by an increased duration of action. It is lipid-soluble and can **exhibit antihypertensive effects without significant diuresis**. Unlike other thiazide compounds, it can be **metabolized by both the GI tract and the kidneys**, which means it would not accumulate in the blood in cases of advanced renal failure.

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Notes