

Thiazide and thiazide-like diuretics

Distal convoluted tubule agents that block the Na^+/Cl^- cotransporter, first-line in primary hypertension, and defined clinically by the electrolyte and metabolic disturbances they produce.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/thiazide-diuretics>

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Quick revision

One Liner: Thiazides block the sodium-chloride cotransporter in the distal convoluted tubule; everything examinable about them follows from that single site - modest natriuresis, potassium and sodium loss, calcium retention and urate retention.

1. Mechanism: blockade of the sodium-chloride (Na^+/Cl^-) channel in the proximal segment of the distal convoluted tubule. [1]
2. Thiazide-type agents include hydrochlorothiazide, chlorothiazide and methyclothiazide; thiazide-like agents include indapamide, metolazone and chlorthalidone. [1]
3. Approved for primary hypertension and for oedema associated with heart failure, hepatic cirrhosis, nephrotic syndrome and several other states. [1]
4. Hypokalaemia arises because increased distal sodium delivery drives aldosterone-mediated potassium and hydrogen ion excretion. [1]
5. Hyponatraemia is a characteristic and clinically important adverse effect, and sodium is one of the standard monitored values. [1]
6. Calcium is retained rather than lost: blocking Na^+/Cl^- increases flow through the $\text{Na}^+/\text{Ca}^{2+}$ exchanger and so increases calcium reabsorption. [1]
7. Urate is retained too, because thiazides directly increase urate reabsorption in the proximal tubule. [1]
8. Efficacy falls as glomerular filtration rate declines, although chlorthalidone, metolazone and indapamide retain effect at low filtration rates. [1]
9. Anuria and sulfonamide allergy are the stated contraindications for this class. [1]

Overview

1. Thiazides are the diuretics of the distal convoluted tubule. Blockade of the sodium-chloride channel in the proximal segment of that tubule prevents sodium reabsorption and promotes natriuresis, and because this segment handles only a modest share of the filtered sodium load, the resulting diuresis is gentler than that of a loop agent. The class divides by chemistry into thiazide-type agents such as hydrochlorothiazide, chlorothiazide and methyclothiazide, and thiazide-like agents such as indapamide, metolazone and chlorthalidone. [1]
2. Approved use covers primary hypertension and oedema associated with congestive heart failure, hepatic cirrhosis, corticosteroid and oestrogen therapy, nephrotic syndrome, acute glomerulonephritis and chronic renal failure. Off-label roles in nephrolithiasis, osteoporosis and diabetes insipidus follow directly from the mechanism, since a drug that increases calcium reabsorption reduces urinary calcium. [1]
3. What shapes prescribing is the biochemical signature rather than the potency. Hypokalaemia, hyponatraemia and metabolic alkalosis sit beside hypercalcaemia, hyperglycaemia, hyperuricaemia and hyperlipidaemia in the documented adverse effect profile, and sodium, potassium, calcium, uric acid and renal function are the values monitored during therapy. Liver injury, by contrast, is exceedingly rare for a class used by millions of people. [1][4]

Classification and drug examples

Intro: Conventionally divided by chemical structure into thiazide-type and thiazide-like agents. The division matters

clinically because duration of action and behaviour at low glomerular filtration rate differ between the two groups even though the tubular target is the same.

1. Name: Thiazide-type diuretics

1. Note: Agents carrying the benzothiadiazine structure; hydrochlorothiazide is the reference member of the group.

1. Name: Hydrochlorothiazide

HCTZ

1. Route: Oral

1. Note: The most widely used member of the group and the usual comparator for the class. [1]

2. Name: Chlorothiazide

2. Route: Oral

2. Note: A thiazide-type agent listed alongside hydrochlorothiazide. [1]

3. Name: Methyclothiazide

3. Route: Oral

3. Note: A further thiazide-type member of the class. [1] [1]

2. Name: Thiazide-like diuretics

2. Note: Structurally distinct agents that act at the same tubular site; these are the members documented to retain efficacy at low glomerular filtration rates.

1. Name: Indapamide

1. Route: Oral

1. Note: Extensively metabolised, and one of the agents that maintains efficacy below 30 mL/min/1.73 m². [1]

2. Name: Chlorthalidone

2. Route: Oral

2. Note: Long acting and about 75% protein bound; also retains efficacy at low filtration rates. [1]

3. Name: Metolazone

3. Route: Oral

3. Note: Hepatically metabolised; the thiazide-like agent most often paired with a loop diuretic for sequential nephron blockade. [1][2] [1]

Mechanism of action

Summary: Thiazides block the sodium-chloride channel in the proximal segment of the distal convoluted tubule, preventing sodium reabsorption there; the downstream consequences of the extra sodium reaching the aldosterone-sensitive nephron account for most of the class's adverse effects.

Target: Sodium-chloride (Na⁺/Cl⁻) channel of the proximal distal convoluted tubule

Cidal Static: not applicable

Kill Kinetics: not applicable

1. Step: 1

1. Title: The Na⁺/Cl⁻ channel is blocked

1. Detail: The drug blocks the sodium-chloride channel in the proximal segment of the distal convoluted tubule, the segment that reabsorbs a modest fraction of the filtered sodium load. [1][2]

2. Step: 2

2. Title: Sodium reabsorption falls and natriuresis follows

2. Detail: Blockade prevents sodium being reabsorbed at that site, promoting natriuresis with water following the retained solute. [1]

3. Step: 3

3. Title: Extra sodium reaches the aldosterone-sensitive segment

3. Detail: The increased sodium delivery activates aldosterone-mediated pumps further along the nephron, and those pumps exchange sodium for potassium and hydrogen ions. [1]

4. Step: 4

4. Title: Potassium and hydrogen ions are lost

4. Detail: That exchange produces the characteristic hypokalaemia and the accompanying metabolic alkalosis, which is why potassium is a monitored value throughout therapy. [1]

5. Step: 5

5. Title: Calcium and urate are retained

5. Detail: Blocking the Na^+/Cl^- channel increases flow through the $\text{Na}^+/\text{Ca}^{2+}$ exchanger so calcium reabsorption rises, and thiazides separately increase urate reabsorption in the proximal tubule. [1]

Major clinical uses

1. Drug: Hydrochlorothiazide

1. Organism: Not applicable

1. Indication: Primary hypertension

1. Line: first-line

1. Note: The best-established indication for the class; choice between agents depends on duration of action and renal function. [1]

2. Drug: Thiazides as a class

2. Organism: Not applicable

2. Indication: Oedema associated with congestive heart failure, hepatic cirrhosis and nephrotic syndrome

2. Line: adjunct

2. Note: Also approved for oedema associated with corticosteroid and oestrogen therapy, acute glomerulonephritis and chronic renal failure. [1]

3. Drug: Thiazides as a class

3. Organism: Not applicable

3. Indication: Recurrent calcium nephrolithiasis (off-label)

3. Line: adjunct

3. Note: Rests on the increase in calcium reabsorption, which reduces the calcium delivered to the urine. [1]

4. Drug: Thiazides as a class

4. Organism: Not applicable

4. Indication: Osteoporosis and diabetes insipidus (off-label)

4. Line: adjunct

4. Note: Both are recorded off-label uses arising from the calcium-retaining and volume effects of the class. [1]

5. Drug: Indapamide

5. Organism: Not applicable

5. Indication: Hypertension where renal function is reduced

5. Line: targeted

5. Note: One of the agents documented to maintain efficacy at glomerular filtration rates below 30 mL/min/1.73 m². [1]

6. Drug: Metolazone

6. Organism: Not applicable

6. Indication: Sequential nephron blockade alongside a loop diuretic in diuretic tolerance

6. Line: reserve

6. Note: A specialist strategy for chronic tolerance to loop therapy; the combined electrolyte risk is substantial. [2]

Pharmacokinetics

1. Drug: Hydrochlorothiazide

1. Route: Oral

1. Absorption: Onset within a few hours of an oral dose, with peak effect in the following hours

1. Csf Penetration: Does not cross the blood-brain barrier; does cross the placenta and appears in breast milk
1. Metabolism: Limited
1. Elimination: Primarily renal
1. Half Life: See prescribing reference
1. Dose Adjust: Efficacy falls as glomerular filtration rate declines [1]
2. Drug: Indapamide
2. Route: Oral
2. Absorption: Oral, with a duration of action longer than the shorter-acting thiazide-type agents
2. Csf Penetration: Not clinically relevant
2. Metabolism: Extensively metabolised
2. Elimination: Primarily renal
2. Half Life: See prescribing reference
2. Dose Adjust: Retains efficacy below 30 mL/min/1.73 m² [1]
3. Drug: Chlorthalidone
3. Route: Oral
3. Absorption: Oral, with the longest duration of action among the commonly used agents
3. Csf Penetration: Not clinically relevant
3. Metabolism: Limited
3. Elimination: Primarily renal
3. Half Life: Long relative to hydrochlorothiazide
3. Dose Adjust: Retains efficacy below 30 mL/min/1.73 m² [1]
1. Onset is recorded at roughly one to two and a half hours with peak effect at two to four hours, while duration ranges from about six to twenty-four hours depending on which agent is used. That spread in duration is the practical difference between the members of the class. [1]
2. Reported elimination half-lives across the class span a wide range, from a few hours to well over a day, and elimination is principally renal with a smaller gastrointestinal contribution. [1]
3. Thiazides cross the placenta and are excreted in breast milk but do not cross the blood-brain barrier, which is relevant to counselling in pregnancy and lactation. [1]
4. This page gives no dose regimens by design. Doses depend on indication, renal function, concurrent therapy and the individual agent, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Hypokalaemia
1. Detail: Follows from the increased distal sodium delivery that drives aldosterone-mediated potassium excretion; potassium is one of the routinely monitored values. [1]
2. Effect: Hyponatraemia
2. Detail: A characteristic disturbance of this class and one of the specified monitoring parameters during therapy. [1]
3. Effect: Metabolic alkalosis
3. Detail: Accompanies the potassium loss, because the same aldosterone-driven exchange also excretes hydrogen ions. [1]
4. Effect: Hyperuricaemia
4. Detail: Thiazides directly increase urate reabsorption in the proximal tubule, so uric acid is monitored alongside the electrolytes. [1]
5. Effect: Hypercalcaemia
5. Detail: Calcium reabsorption rises because blockade of the Na⁺/Cl⁻ channel increases flow through the Na⁺/Ca²⁺ exchanger. [1]
6. Effect: Hyperglycaemia and hyperlipidaemia

6. Detail: Both are recorded metabolic adverse effects of thiazide therapy. [1]

1. Effect: Hypersensitivity reactions in sulfonamide allergy

1. Detail: Sulfonamide allergy is a recorded contraindication for the class, and hypersensitivity reactions are among the rare adverse reactions described.

1. Action: Establish the allergy history before a thiazide is selected and consider a structurally different diuretic. [1][4]

2. Effect: Pancreatitis

2. Detail: Listed among the rare adverse reactions associated with thiazide diuretics.

2. Action: Investigate abdominal pain with the possibility in mind rather than attributing it to the underlying illness. [4]

3. Effect: Clinically apparent liver injury

3. Detail: Exceedingly rare despite very wide use; reported enzyme patterns have ranged from hepatocellular through mixed to cholestatic, with a short latency of days to several weeks and rapid recovery on withdrawal.

3. Action: Recognised as a rare event rather than a reason for routine liver monitoring in this class. [4]

1. Drug: Hydrochlorothiazide

1. Effect: Carries the highest liver-injury likelihood rating within the class, though the event remains rare. [4]

2. Drug: Chlorthalidone, metolazone and indapamide

2. Effect: Retain diuretic and antihypertensive efficacy at glomerular filtration rates below 30 mL/min/1.73 m², unlike the class as a whole. [1]

Contraindications, precautions and interactions

1. Anuria, since a diuretic acting on tubular sodium handling cannot work and volume depletion is the only likely result. [1]

2. Sulfonamide allergy, recorded as a contraindication for thiazide diuretics. [1]

1. Reduced glomerular filtration rate, where most members of the class lose effectiveness even though selected thiazide-like agents do not. [1]

2. Diabetes and established gout, given the documented hyperglycaemia and hyperuricaemia associated with therapy. [1]

3. Pregnancy and lactation, because the drug crosses the placenta and is excreted in breast milk. [1]

4. Older patients and those with cardiac, hepatic, renal or metabolic disease, in whom fluid status, electrolytes, weight, acid-base status, glucose and blood pressure warrant particularly careful assessment. [2]

1. With: Loop diuretics

1. Effect: Deliberate combination produces sequential nephron blockade in diuretic tolerance, at the cost of compounding the electrolyte disturbance. [2]

2. With: Potassium-sparing diuretics and renin-angiotensin system inhibitors

2. Effect: Co-prescription is used to offset thiazide-induced hypokalaemia, but shifts the risk towards hyperkalaemia and needs potassium monitoring in both directions. [2]

Resistance mechanisms

1. Mechanism: Falling glomerular filtration rate

1. Detail: Thiazide diuretics lose effectiveness for both diuresis and blood pressure reduction as glomerular filtration rate declines, which is the commonest reason a previously effective agent stops working.

Advancing chronic kidney disease

1. Countermeasure: Chlorthalidone, metolazone and indapamide are documented to maintain efficacy at filtration rates below 30 mL/min/1.73 m². [1]

2. Mechanism: Distal tubular structural adaptation

2. Detail: Chronic diuretic exposure allows the kidney to adapt structurally so that sodium retention increases, blunting the response over time.

Long-term diuretic therapy in heart failure

2. Countermeasure: Sequential nephron blockade, in which a thiazide-like agent is combined with a loop diuretic to block the adapted segment as well. [2]
3. Mechanism: Continued high dietary sodium intake
3. Detail: Sodium taken in between doses replaces what the drug removed, and dietary salt restriction is named among the measures that overcome acute tolerance to diuretic therapy.
- Unrestricted salt intake during antihypertensive therapy
3. Countermeasure: Attention to the timing of diet and to dietary salt restriction alongside the choice of agent. [2]
- Stewardship Note: Failure of a diuretic to increase urine output is treated as a signal to stop and reassess rather than to escalate, because it can indicate undiagnosed underlying renal pathology.

Comparison tables

Title: Thiazide versus loop diuretics at a glance

Caption: The two classes differ by nephron site, and almost every other difference follows from that. Therapy choice belongs to the treating clinician working from a current prescribing reference.

1. Key: feature
1. Label: Feature
1. Is Row Header: true
2. Key: thiazide
2. Label: Thiazide / thiazide-like
3. Key: loop
3. Label: Loop
1. Feature: Nephron site
1. Thiazide: Proximal segment of the distal convoluted tubule
1. Loop: Thick ascending limb of the loop of Henle [1][3]
2. Feature: Transporter blocked
2. Thiazide: Na⁺/Cl⁻ channel
2. Loop: Na-K-2Cl (NKCC2) cotransporter [1][3]
3. Feature: Effect on serum calcium
3. Thiazide: Increases calcium reabsorption; hypercalcaemia
3. Loop: Causes loss of calcium and magnesium [1][3]
4. Feature: Behaviour at low filtration rate
4. Thiazide: Effectiveness falls, except chlorthalidone, metolazone and indapamide
4. Loop: Remains the agent used in renal disease-associated oedema [1][3]
5. Feature: Ototoxicity
5. Thiazide: Not a feature of this class
5. Loop: A specific adverse effect of loop agents, not shared by other diuretics [2]

High-yield exam pearls

1. Pearl: Thiazides keep calcium, loops lose it.
1. Why: Blocking the Na⁺/Cl⁻ channel increases flow through the Na⁺/Ca²⁺ exchanger and therefore calcium reabsorption, which is why hypercalcaemia is a thiazide effect and why the class is used off-label in nephrolithiasis and osteoporosis. [1]
2. Pearl: The hypokalaemia is indirect, not a direct potassium channel effect.
2. Why: More sodium reaching the distal nephron activates aldosterone-mediated pumps that trade sodium for potassium and hydrogen ions, which produces both the hypokalaemia and the metabolic alkalosis. [1]
3. Pearl: Two hypers and two hypos summarise the metabolic profile.
3. Why: Hyperglycaemia, hyperuricaemia, hyperlipidaemia and hypercalcaemia sit alongside hypokalaemia and

hyponatraemia in the documented adverse effect list, and remembering them as a set covers most examination questions. [1]

4. Pearl: Not every agent fails at a low filtration rate.

4. Why: The class as a whole loses diuretic and antihypertensive effect as glomerular filtration rate falls, yet chlorthalidone, metolazone and indapamide are documented to maintain efficacy below 30 mL/min/1.73 m². [1]

5. Pearl: Sulfonamide allergy is a class-level contraindication here.

5. Why: Anuria and sulfonamide allergy are the two contraindications recorded for thiazides, so an allergy history changes the choice of diuretic rather than merely the monitoring plan. [1]

6. Pearl: Adding a thiazide-like agent to a loop diuretic is a deliberate strategy, not a duplication.

6. Why: Co-administering a thiazide-like diuretic with a loop diuretic produces sequential nephron blockade, one of the documented approaches to chronic tolerance to loop therapy. [2]

Common exam traps

1. Trap: "Thiazides act on the loop of Henle."

1. Correction: They act in the proximal segment of the distal convoluted tubule. The thick ascending limb of the loop of Henle is the loop diuretic site. [1][2]

2. Trap: "All diuretics waste calcium."

2. Correction: Thiazides increase calcium reabsorption and can cause hypercalcaemia, which is the opposite of the calcium loss seen with loop agents. [1][3]

3. Trap: "A thiazide is useless once renal function is poor."

3. Correction: Effectiveness does fall as glomerular filtration rate declines, but chlorthalidone, metolazone and indapamide are documented to keep working at filtration rates below 30 mL/min/1.73 m². [1]

4. Trap: "Thiazides lower uric acid because they increase urine flow."

4. Correction: They raise it. Thiazides directly increase urate reabsorption in the proximal tubule, and hyperuricaemia is a listed adverse effect. [1]

Self-test questions

1. Question: Where in the nephron do thiazide diuretics act, and what do they block?

1. The thick ascending limb, blocking the Na-K-2Cl cotransporter

2. The proximal segment of the distal convoluted tubule, blocking the Na⁺/Cl⁻ channel

3. The collecting duct, blocking the epithelial sodium channel

4. The proximal tubule, inhibiting carbonic anhydrase

1. Explanation: The defining action is blockade of the sodium-chloride channel in the proximal segment of the distal convoluted tubule. The Na-K-2Cl cotransporter of the thick ascending limb belongs to loop diuretics, and the epithelial sodium channel of the collecting duct belongs to the potassium-sparing agents. [1][2]

2. Question: Why does thiazide therapy tend to lower serum potassium?

1. The drug blocks potassium reabsorption directly in the distal convoluted tubule

2. Increased sodium delivery to the distal nephron activates aldosterone-mediated pumps that excrete potassium and hydrogen ions

3. Thiazides inhibit the sodium-potassium ATPase in every tubular segment

4. Potassium is displaced from plasma protein binding sites by the drug

2. Explanation: The potassium loss is a downstream consequence. Sodium that escapes reabsorption in the distal convoluted tubule reaches the aldosterone-sensitive segment, where sodium uptake is coupled to potassium and hydrogen ion secretion, which also explains the accompanying metabolic alkalosis. [1]

3. Question: Which serum abnormality is characteristic of thiazides but NOT of loop diuretics?

1. Hypokalaemia

2. Metabolic alkalosis

3. Hypercalcaemia

4. Hyperuricaemia

3. Explanation: Thiazide blockade of the Na^+/Cl^- channel increases flow through the $\text{Na}^+/\text{Ca}^{2+}$ exchanger and therefore calcium reabsorption, so calcium rises. Loop diuretics do the opposite and cause loss of calcium and magnesium. Hypokalaemia, alkalosis and hyperuricaemia occur with both. [1][3]

4. Question: A patient on a thiazide develops a first attack of gout. What is the pharmacological explanation?

1. Thiazides directly increase urate reabsorption in the proximal tubule

2. Thiazides inhibit xanthine oxidase and cause urate to accumulate

3. Thiazides increase urate production by accelerating purine turnover

4. Thiazides block urate secretion into bile

4. Explanation: Hyperuricaemia is a recognised thiazide adverse effect, and the recorded mechanism is a direct increase in urate reabsorption in the proximal tubule. Uric acid is therefore one of the values monitored during therapy.

[1]

5. Question: Which statement about thiazides in reduced renal function is correct?

1. All thiazides retain full efficacy regardless of glomerular filtration rate

2. The class loses effectiveness as filtration rate falls, but chlorthalidone, metolazone and indapamide maintain efficacy at low filtration rates

3. Thiazides are the preferred diuretic in anuria

4. Thiazides increase glomerular filtration rate and so become more effective as renal function worsens

5. Explanation: Diuretic and antihypertensive effect declines across the class as glomerular filtration rate falls, but chlorthalidone, metolazone and indapamide are documented exceptions that keep working below $30 \text{ mL/min/1.73 m}^2$. Anuria is a contraindication, not an indication. [1]

Anuria is a contraindication, not an indication. [1]

6. Question: Which pair represents the recorded contraindications to thiazide diuretics?

1. Pregnancy and asthma

2. Anuria and sulfonamide allergy

3. Hyperkalaemia and myasthenia gravis

4. Peptic ulcer disease and glaucoma

6. Explanation: Anuria and sulfonamide allergy are the contraindications recorded for the class. Because the parent structure is a sulfonamide, an allergy history redirects the choice of diuretic rather than simply intensifying monitoring.

[1]

7. Question: Why might a thiazide-like diuretic be added to an established loop diuretic rather than substituted for it?

1. To reduce the ototoxic risk of the loop agent

2. To achieve sequential nephron blockade, one of the documented responses to chronic tolerance to loop diuretics

3. Because thiazides reverse the metabolic alkalosis caused by loop diuretics

4. Because thiazides prevent the hyperuricaemia caused by loop diuretics

7. Explanation: Chronic tolerance to loop diuretics reflects distal tubular structural adaptation, and co-administering a thiazide-like diuretic blocks that adapted segment as well - a deliberate sequential blockade. It intensifies rather than corrects the shared electrolyte risks, so monitoring becomes more, not less, important. [2]

Frequently asked questions

1. Question: Why are thiazides described as weaker diuretics than loop agents?

1. Answer: Because of where they act. The distal convoluted tubule handles a smaller share of the filtered sodium load than the thick ascending limb, so blocking it produces a smaller natriuresis. That is also why thiazides suit long-term blood pressure control better than acute decongestion. [1][2]

2. Question: Why do thiazides raise calcium when loop diuretics lower it?

2. Answer: Blocking the Na^+/Cl^- channel increases flow through the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, so more calcium is reabsorbed. Loop diuretics interfere with the electrical gradient in the thick ascending limb instead, and calcium and

magnesium are lost. [1][3]

3. Question: Which laboratory values are followed during thiazide therapy?

3. Answer: Sodium, potassium, uric acid and calcium are the specified values, with renal function assessed alongside them. Fluid status, weight, acid-base status, glucose and blood pressure are also part of routine diuretic assessment. [1][2]

4. Question: Does a sulfonamide antibiotic allergy rule out a thiazide?

4. Answer: Sulfonamide allergy is recorded as a contraindication for this class, so the allergy history is established before a thiazide is chosen. Where a diuretic is still needed, a structurally different agent is considered by the treating clinician. [1]

5. Question: Are thiazides hard on the liver?

5. Answer: No. Only rare instances of clinically apparent liver injury have been linked to thiazide diuretics despite use in very large populations, and when it has occurred, latency was short and recovery on withdrawal was rapid. [4]

References

[1] Thiazide Diuretics (StatPearls). StatPearls Publishing / NCBI Bookshelf 2026.

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