

Potassium-sparing diuretics

Weak diuretics acting on the aldosterone-sensitive distal nephron that conserve potassium instead of wasting it, valued as partners to stronger agents and defined clinically by hyperkalaemia risk.

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

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Quick revision

One Liner: Potassium-sparing diuretics act on the aldosterone-sensitive distal nephron, which handles only about 3% of the filtered sodium load - so they are weak diuretics whose real value is what they do to potassium, and hyperkalaemia is the price.

1. Site of action is the aldosterone-sensitive distal nephron, comprising the late distal convoluted tubule, connecting tubules and collecting ducts. [1]
2. That segment reabsorbs only around 3% of the filtered sodium load, which is why these agents are weak diuretics used mainly in combination. [1]
3. Two mechanisms exist: direct epithelial sodium channel blockade by amiloride and triamterene, and mineralocorticoid receptor antagonism by spironolactone and eplerenone. [1]
4. Hyperkalaemia and hyperchloraemic metabolic acidosis are the most common adverse effects, following directly from suppressed potassium secretion. [1]
5. Amiloride carries a boxed warning for hyperkalaemia, which may be fatal in susceptible patients. [2]
6. The class is contraindicated in hyperkalaemia until the underlying cause is corrected, and in advanced renal impairment. [1]
7. Amiloride acts independently of aldosterone, which is why it is less effective than the receptor antagonists in hyperaldosteronism. [2]
8. Triamterene is specifically associated with nephrolithiasis, crystalline tubular deposition and drug-induced interstitial nephritis. [3]
9. Amiloride is the treatment of choice in Liddle syndrome, where the epithelial sodium channel itself is overactive. [1]

Overview

1. Potassium-sparing diuretics act on the aldosterone-sensitive distal nephron - the late distal convoluted tubule, the connecting tubules and the collecting ducts. This segment reabsorbs only about 3% of the filtered sodium load, so these are weak diuretics by design. Their clinical value lies in the direction they push potassium, which is the opposite of what thiazide and loop agents do. [1]
2. The class contains two mechanistically distinct groups. Amiloride and triamterene bind epithelial sodium channels in the principal cells and suppress them directly. Spironolactone and eplerenone act one step earlier, suppressing the aldosterone-induced proteins that increase production, redistribution and activation of those same channels; their receptor pharmacology, prognostic role in heart failure and endocrine adverse effects are covered in the mineralocorticoid receptor antagonists class. [1]
3. Hyperkalaemia dominates the safety picture. It is the most common adverse effect together with hyperchloraemic metabolic acidosis, it is the reason the class is contraindicated in existing hyperkalaemia and in advanced renal impairment, and it is the subject of a boxed warning on amiloride. Liver injury, by contrast, is only rarely associated with any diuretic. [1][2][4]

Classification and drug examples

Intro: Divided by where the drug intervenes: at the channel itself, or at the receptor that regulates it. Both routes reduce

sodium reabsorption in the aldosterone-sensitive distal nephron and both conserve potassium, but they differ in whether aldosterone must be present for the drug to matter.

1. Name: Epithelial sodium channel blockers

1. Note: Bind epithelial sodium channels in the principal cells of the aldosterone-sensitive distal nephron and suppress them directly, independently of aldosterone.

1. Name: Amiloride

1. Route: Oral

1. Note: Not metabolised by the liver and excreted largely unchanged by the kidneys; carries a boxed warning for hyperkalaemia. [2]

2. Name: Triamterene

2. Route: Oral

2. Note: Frequently combined with hydrochlorothiazide; carries agent-specific risks of nephrolithiasis and interstitial nephritis. [3] [1]

2. Name: Mineralocorticoid receptor antagonists (covered in their own class)

2. Note: Included here for completeness because they are conventionally counted among the potassium-sparing diuretics. They act indirectly, by suppressing the aldosterone-induced proteins that increase production, redistribution and activation of epithelial sodium channels. Their receptor pharmacology, heart-failure role and endocrine adverse effects belong to the mineralocorticoid receptor antagonists page rather than this one.

1. Name: Spironolactone

1. Route: Oral

1. Note: Also used in androgen-excess syndromes such as hirsutism, and more effective than amiloride where aldosterone excess is the driver. [1][2]

2. Name: Eplerenone

2. Route: Oral

2. Note: Used in primary aldosteronism among its recorded indications. [1] [1]

Mechanism of action

Summary: These agents reduce sodium reabsorption in the aldosterone-sensitive distal nephron, either by blocking the epithelial sodium channel directly or by removing the aldosterone signal that maintains it; reduced sodium entry removes the electrical driving force for potassium secretion, which is why potassium is conserved.

Target: Epithelial sodium channel (ENaC) of the principal cells of the aldosterone-sensitive distal nephron

Cidal Static: not applicable

Kill Kinetics: not applicable

1. Step: 1

1. Title: The drug reaches the aldosterone-sensitive distal nephron

1. Detail: The relevant segment comprises the late distal convoluted tubule, the connecting tubules and the collecting ducts, and accounts for the reabsorption of about 3% of the filtered sodium load. [1]

2. Step: 2

2. Title: Epithelial sodium channels are suppressed

2. Detail: Amiloride and triamterene bind those channels in the principal cells and suppress them directly, while receptor antagonists reduce the aldosterone-driven production and activation of the same channels. [1]

3. Step: 3

3. Title: Sodium reabsorption falls and a modest natriuresis follows

3. Detail: Because the segment handles only a small share of filtered sodium, the diuretic effect is limited, which is why these agents are usually partners to a stronger diuretic rather than a replacement for one. [1]

4. Step: 4

4. Title: The gradient driving potassium secretion is lost

4. Detail: Reduced sodium entry lessens apical membrane depolarisation, which decreases the secretion of potassium and also of hydrogen, calcium and magnesium ions. [2]

5. Step: 5

5. Title: Potassium and hydrogen ions are retained

5. Detail: The retained potassium is the therapeutic point of the class, and the retained hydrogen ion is why hyperchloraemic metabolic acidosis accompanies hyperkalaemia as a characteristic adverse effect. [1]

Major clinical uses

1. Drug: Amiloride

1. Organism: Not applicable

1. Indication: Adjunctive therapy with a thiazide or loop diuretic in heart failure and hypertension, to restore or protect serum potassium

1. Line: adjunct

1. Note: The principal approved role of the epithelial sodium channel blockers is preventing or correcting diuretic-induced hypokalaemia. [2]

2. Drug: Amiloride

2. Organism: Not applicable

2. Indication: Prevention of hypokalaemia in patients receiving digoxin or with significant arrhythmias

2. Line: adjunct

2. Note: An approved indication that reflects how dangerous potassium depletion is in those specific settings. [2]

3. Drug: Amiloride

3. Organism: Not applicable

3. Indication: Liddle syndrome, and off-label in lithium-induced nephrogenic diabetes insipidus

3. Line: targeted

3. Note: Liddle syndrome is a disorder of the channel itself, which is why direct blockade is described as the treatment of choice. [1][2]

4. Drug: Triamterene

4. Organism: Not applicable

4. Indication: Oedematous states including heart failure, nephrotic kidney disease, cirrhosis, secondary hyperaldosteronism and idiopathic oedema

4. Line: adjunct

4. Note: Also combined with hydrochlorothiazide for hypertension and for patients who become hypokalaemic on the thiazide alone. [3]

5. Drug: Potassium-sparing diuretics as a class

5. Organism: Not applicable

5. Indication: Correction of hypokalaemia and hypomagnesaemia induced by other diuretics

5. Line: adjunct

5. Note: The defining combination use, and the reason these weak agents remain in the formulary. [1]

6. Drug: Spironolactone and eplerenone

6. Organism: Not applicable

6. Indication: Aldosterone-driven states, including primary aldosteronism, and androgen-excess syndromes such as hirsutism

6. Line: targeted

6. Note: Detailed pharmacology of these agents is covered in the mineralocorticoid receptor antagonists class rather than repeated here. [1]

Pharmacokinetics

1. Drug: Amiloride

1. Route: Oral

1. Absorption: Onset around two hours after an oral dose, with peak plasma concentrations at three to four hours

1. Csf Penetration: Not clinically relevant

1. Metabolism: Not metabolised by the liver

1. Elimination: About half excreted unchanged in urine and about 40% in faeces

1. Half Life: Approximately 6 to 9 hours with normal renal function

1. Dose Adjust: Contraindicated in renal insufficiency and avoided at low filtration rates [2]

2. Drug: Eplerenone

2. Route: Oral

2. Absorption: See prescribing reference

2. Csf Penetration: Not clinically relevant

2. Metabolism: See prescribing reference

2. Elimination: See prescribing reference

2. Half Life: See prescribing reference

2. Dose Adjust: Governed by potassium and renal function; detailed handling is covered in the mineralocorticoid receptor antagonists class [1]

1. Amiloride is unusual in bypassing hepatic metabolism altogether, which concentrates the consequences of impaired elimination in the kidney and explains why renal impairment converts a manageable drug into a hazardous one. [2]

2. Monitoring for this class centres on serum potassium, urea and creatinine, with blood pressure, daily weight, serum bicarbonate and magnesium also followed. [2]

3. For triamterene the recommended baseline and periodic checks include urea and creatinine, blood pressure, urine output, serum uric acid, full blood count and electrolytes with particular attention to potassium. [3]

4. This page gives no dose regimens by design. Doses depend on the partner diuretic, renal function, potassium concentration and indication, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Hyperkalaemia

1. Detail: The most common adverse effect of the class, arising from inhibition of epithelial sodium channels and consequently suppressed potassium secretion. [1]

2. Effect: Hyperchloraemic metabolic acidosis

2. Detail: Accompanies the hyperkalaemia, because hydrogen ion secretion falls for the same electrical reason that potassium secretion does. [1]

3. Effect: Gastrointestinal and general symptoms

3. Detail: Nausea, vomiting, diarrhoea and headache are the commonest reported reactions to amiloride, with fatigue, muscle cramps and dizziness also described. [2]

4. Effect: Dizziness, fatigue, dry mouth and dehydration

4. Detail: Reported among the main adverse effects of triamterene alongside hyperkalaemia. [3]

1. Effect: Fatal hyperkalaemia

1. Detail: Amiloride carries a boxed warning for hyperkalaemia, whether used alone or in a fixed combination with hydrochlorothiazide, and the warning states the disturbance may be fatal.

1. Action: Serum potassium is checked before and during therapy, and the drug is withheld where potassium is already raised. [2]

2. Effect: Acute renal failure from triamterene crystalline deposition

2. Detail: Triamterene can deposit as crystals in the renal tubules and cause acute renal failure, and is separately

linked to drug-induced interstitial nephritis.

2. Action: Renal function and urine output are followed, and a stone history changes the risk assessment. [3]

3. Effect: Nephrolithiasis and urolithiasis

3. Detail: Triamterene stone formation is described particularly in patients with a history of previous kidney stones.

3. Action: Take the stone history into account before selecting this agent over an alternative. [3]

1. Drug: Amiloride

1. Effect: Aldosterone-independent channel blockade, and documented to be less effective than spironolactone and eplerenone in hyperaldosteronism. [2]

2. Drug: Diuretics generally, including amiloride, spironolactone and triamterene

2. Effect: Implicated in rare cases of drug-induced liver injury; clinically apparent injury from diuretics as a whole is rare. [4]

Contraindications, precautions and interactions

1. Existing hyperkalaemia, until the underlying pathology has been corrected. [1]

2. Advanced renal failure or chronic kidney disease, particularly at a filtration rate below 30 mL/min/1.73 m². [1]

3. For amiloride specifically: anuria, acute or chronic renal insufficiency, concurrent use of another potassium-sparing diuretic, and hypersensitivity. [2]

4. For triamterene specifically: hyperkalaemia, pregnancy, severe hepatic impairment, severe renal impairment, metabolic or respiratory acidosis, acute myopia and secondary angle-closure glaucoma. [3]

1. Diabetes and older age, both described as raising the hyperkalaemia risk with amiloride. [2]

2. A history of kidney stones, given the specific association between triamterene and nephrolithiasis. [3]

3. Any situation where potassium is already being retained by another mechanism, since the effects are additive rather than independent. [1]

1. With: ACE inhibitors, angiotensin receptor blockers, beta blockers, NSAIDs and aliskiren

1. Effect: Each causes some potassium retention, so concurrent use with a potassium-sparing diuretic may cause hyperkalaemia and is treated as a relative contraindication. [1]

2. With: Another potassium-sparing diuretic

2. Effect: Listed as a contraindication for amiloride, because the hyperkalaemia risks compound without a corresponding gain in diuresis. [2]

3. With: Thiazide and loop diuretics

3. Effect: The intended partnership: the potassium-wasting agent supplies the diuresis and the potassium-sparing agent offsets the potassium loss. [1]

Comparison tables

Title: Channel blockers versus receptor antagonists

Caption: Both groups conserve potassium, but only one depends on aldosterone being present. Therapy choice and dosing belong to the treating clinician working from a current prescribing reference.

1. Key: feature

1. Label: Feature

1. Is Row Header: true

2. Key: enac

2. Label: Amiloride / triamterene

3. Key: mra

3. Label: Spironolactone / eplerenone

1. Feature: Point of action

1. Enac: The epithelial sodium channel itself, in principal cells

1. Mra: The aldosterone-induced proteins that produce, redistribute and activate that channel [1]

- 2. Feature: Aldosterone dependence
- 2. Enac: Independent of aldosterone
- 2. Mra: Depends on aldosterone signalling being present [2][1]
- 3. Feature: Relative effect in hyperaldosteronism
- 3. Enac: Amiloride is less effective in this setting
- 3. Mra: The more effective option where aldosterone excess drives the problem [2]
- 4. Feature: Signature agent-specific risk
- 4. Enac: Boxed warning for hyperkalaemia (amiloride); crystalluria, stones and interstitial nephritis (triamterene)
- 4. Mra: Covered in the mineralocorticoid receptor antagonists class [2][3]
- 5. Feature: Shared hazard
- 5. Enac: Hyperkalaemia with hyperchloraemic metabolic acidosis
- 5. Mra: Hyperkalaemia with hyperchloraemic metabolic acidosis [1]

High-yield exam pearls

- 1. Pearl: Two routes to the same channel.
- 1. Why: Amiloride and triamterene bind the epithelial sodium channel directly, whereas spironolactone and eplerenone suppress the aldosterone-induced proteins that increase production, redistribution and activation of that channel. The end point is shared; the point of attack is not. [1]
- 2. Pearl: The potassium effect is electrical, not a separate drug action.
- 2. Why: Blocking sodium entry reduces the depolarisation of the apical membrane that normally drives potassium secretion, so potassium - along with hydrogen, calcium and magnesium - is retained rather than lost. [2]
- 3. Pearl: Aldosterone-dependence separates amiloride from spironolactone.
- 3. Why: Amiloride blocks the channel whether or not aldosterone is driving it, but it is documented to be less effective than spironolactone and eplerenone in hyperaldosteronism, where the receptor is the rational target. [2]
- 4. Pearl: Renal function sets the ceiling for this class.
- 4. Why: These agents are contraindicated in advanced renal failure or chronic kidney disease because of hyperkalaemia risk, and this is stated to be particularly true below a filtration rate of 30 mL/min/1.73 m². [1]
- 5. Pearl: Triamterene has a renal signature the others do not.
- 5. Why: Crystalline deposition in the renal tubules, nephrolithiasis in patients with a stone history and drug-induced interstitial nephritis are described specifically for triamterene rather than for the class as a whole. [3]
- 6. Pearl: Combining with a renin-angiotensin system inhibitor is a relative contraindication, not a neutral pairing.
- 6. Why: ACE inhibitors, angiotensin receptor blockers, beta blockers, NSAIDs and aliskiren all cause some potassium retention, so adding a potassium-sparing diuretic can tip a patient into hyperkalaemia. [1]

Common exam traps

- 1. Trap: "Potassium-sparing diuretics are a good way to get a large diuresis."
- 1. Correction: They are weak diuretics. The aldosterone-sensitive distal nephron reabsorbs only about 3% of the filtered sodium load, so their main role is correcting or preventing the hypokalaemia caused by stronger agents. [1]
- 2. Trap: "Amiloride and spironolactone work the same way."
- 2. Correction: Amiloride binds the epithelial sodium channel directly and acts independently of aldosterone; spironolactone works through the mineralocorticoid receptor and is the more effective agent when aldosterone excess is the problem. [1][2]
- 3. Trap: "Hyperkalaemia with these drugs is a laboratory curiosity."
- 3. Correction: Amiloride carries a boxed warning stating that hyperkalaemia may be fatal, and risk is highest in diabetes, older patients and renal impairment. [2]
- 4. Trap: "Any potassium-sparing agent can be added to another one for extra effect."
- 4. Correction: Concurrent use of a second potassium-sparing diuretic is listed among the contraindications to

amiloride, precisely because the hyperkalaemia risks compound. [2]

Self-test questions

1. Question: Which nephron segment do potassium-sparing diuretics act on?

1. The proximal convoluted tubule
2. The thick ascending limb of the loop of Henle
3. The aldosterone-sensitive distal nephron: late distal convoluted tubule, connecting tubules and collecting ducts
4. The glomerulus

1. Explanation: The target is the aldosterone-sensitive distal nephron. Because that segment accounts for the reabsorption of only about 3% of the filtered sodium load, the diuretic effect is small and the potassium effect is what makes the class useful. [1]

2. Question: How does amiloride differ mechanistically from spironolactone?

1. Amiloride blocks the epithelial sodium channel directly and works independently of aldosterone
2. Amiloride is a mineralocorticoid receptor antagonist and spironolactone blocks the channel
3. Amiloride inhibits carbonic anhydrase in the collecting duct
4. Amiloride and spironolactone both bind the mineralocorticoid receptor with different affinities

2. Explanation: Amiloride binds epithelial sodium channels in the principal cells and suppresses them directly, without depending on aldosterone. Receptor antagonists instead suppress the aldosterone-induced proteins that increase production, redistribution and activation of those channels. [1][2]

3. Question: Why does blocking the epithelial sodium channel raise serum potassium?

1. The drug directly stimulates potassium reabsorption in the proximal tubule
2. Reduced sodium entry lessens the apical membrane depolarisation that drives potassium secretion
3. The drug displaces potassium from intracellular stores
4. The drug inhibits renal potassium filtration at the glomerulus

3. Explanation: Sodium entry through the channel is what depolarises the apical membrane and creates the gradient for potassium secretion. Blocking it therefore reduces secretion not only of potassium but also of hydrogen, calcium and magnesium ions. [2]

4. Question: In which patient group is this class contraindicated because of hyperkalaemia risk?

1. Patients with hypokalaemia on a thiazide
2. Patients with advanced renal failure or chronic kidney disease, particularly below 30 mL/min/1.73 m²
3. Patients with primary aldosteronism
4. Patients with Liddle syndrome

4. Explanation: Advanced renal impairment is the stated contraindication, and the risk is described as particularly relevant below a filtration rate of 30 mL/min/1.73 m². Hypokalaemia from another diuretic, aldosteronism and Liddle syndrome are all reasons the class is used, not withheld. [1]

5. Question: Which agent is described as the treatment of choice in Liddle syndrome?

1. Spironolactone
2. Eplerenone
3. Amiloride
4. Hydrochlorothiazide

5. Explanation: Liddle syndrome is a disorder of the epithelial sodium channel itself, so direct channel blockade addresses the defect. Mineralocorticoid receptor antagonists act one step upstream and are the rational choice in aldosterone excess instead. [1]

6. Question: Which renal complication is described specifically for triamterene?

1. Papillary necrosis
2. Crystalline deposition in the renal tubules with nephrolithiasis and interstitial nephritis
3. Renal artery stenosis

4. Minimal change nephropathy

6. Explanation: Triamterene is linked to nephrolithiasis in patients with a stone history, to urolithiasis, to crystalline deposition in renal tubules causing acute renal failure, and to drug-induced interstitial nephritis. These are agent-specific rather than class effects. [3]

7. Question: Which combination raises hyperkalaemia risk enough to be treated as a relative contraindication?

1. A potassium-sparing diuretic with a renin-angiotensin system inhibitor, beta blocker, NSAID or aliskiren
2. A potassium-sparing diuretic with a thiazide
3. A potassium-sparing diuretic with a loop diuretic
4. A potassium-sparing diuretic with a statin

7. Explanation: Each of those agents causes some degree of potassium retention on its own, so adding a potassium-sparing diuretic can produce hyperkalaemia. Pairing with a thiazide or a loop diuretic is the standard use of the class, since those agents waste potassium. [1]

Frequently asked questions

1. Question: Why are these called potassium-sparing rather than potassium-raising diuretics?

1. Answer: Because the effect is a failure to excrete rather than an active reclamation. Blocking sodium entry removes the electrical driving force for potassium secretion, so potassium stays where it is instead of being lost in the urine. [2]

2. Question: Why are they so often prescribed with another diuretic rather than alone?

2. Answer: Their site of action handles only about 3% of the filtered sodium load, so used alone they produce little diuresis. Paired with a thiazide or loop agent, they supply the potassium protection that the stronger drug takes away. [1]

3. Question: What makes hyperkalaemia so dangerous with this class?

3. Answer: It can be fatal. Amiloride carries a boxed warning to that effect, and risk is highest in diabetes, older patients and anyone with reduced renal function, which is why potassium and renal function are checked before and during therapy. [2]

4. Question: Where do spironolactone and eplerenone fit?

4. Answer: They are conventionally counted among the potassium-sparing diuretics because they conserve potassium at the same nephron segment, but they act through the mineralocorticoid receptor. Their receptor pharmacology, heart-failure role and endocrine effects are set out in the mineralocorticoid receptor antagonists class. [1]

5. Question: Is triamterene interchangeable with amiloride?

5. Answer: Mechanistically they are close, since both block the epithelial sodium channel. Clinically they differ: triamterene carries specific risks of crystalline tubular deposition, stones and interstitial nephritis that are not described for amiloride. [3][2]

References

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